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(54) Title: NOVEL AMINO ACID PRODRUG RENIN INHIBITORS

(57) Abstract

Novel amino acid prodrug renin inhibitors are described, as well as methods for the preparation and pharmaceutical compositions of the same, which are useful as renin inhibitors and thus useful in controlling hypertension, hyperaldosteronism, congestive heart failure, and glaucoma, as well as diagnostic agents.

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# NOVEL AMINO ACID PRODRUG RENIN INHIBITORS

## BACKGROUND OF THE INVENTION

The present invention relates to novel amino acid prodrug renin inhibitors useful as pharmaceutical agents, to methods for their production, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment as well as the use of these agents as diagnostic tools. More particularly, the novel compounds of the present invention inhibit the enzyme renin thus controlling hypertension, hyperaldosteronism, congestive heart failure, and glaucoma as well as the use of the compounds as diagnostic tools in mammals.

Renin is a natural enzyme which is released into the blood stream from the kidney. It cleaves its natural substrate, angiotensinogen, releasing a decapeptide, angiotensin I. This in turn is cleaved by converting enzyme in the lung, kidney, and other tissues to an octapeptide, angiotensin II. Angiotensin II raises blood pressure both directly by causing arteriolar constriction and indirectly by stimulating release of the sodium-retaining hormone aldosterone from the adrenal gland causing a rise in extracellular fluid volume. Inhibitors of renin have been sought as agents for control of hypertension and hyperaldosteronism.

Additionally, since HIV protease, like renin, is an aspartyl protease, the novel compounds of the present invention also can be used to treat disorders caused by retroviruses including HTLV I, II, and III.

Renin inhibitors have been shown to be effective agents in the control of hypertension and related

cardiovascular diseases. However, in general they suffer the drawbacks of poor aqueous solubility and bioavailability. Thus, there is a need to develop a renin inhibitor that has good aqueous solubility and bioavailability.

We have found unexpectedly that certain amino acid derivatives of renin inhibitors have increased water solubility and bioavailability. These derivatives are stable in the gastrointestinal tract but undergo selective, enzyme catalyzed cleavage of the amino acid auxiliary at the gut wall to produce a high local concentration of the parent renin inhibitor and hence improved transport across the gut wall. This effect, combined with the much higher gut lumen concentration of compound due to increased solubility, greatly enhances oral adsorption and hence overall bioavailability. Some of the parent compounds have been disclosed in United States Patent U.S. 5,036,053, European Published Application EP 0399,556, and Repine, J. T., et al, Journal of Medicinal Chemistry, Volume 34, pages 1935-1943 (1991) as renin inhibitors.

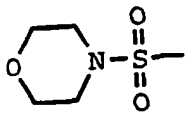
## SUMMARY OF THE INVENTION

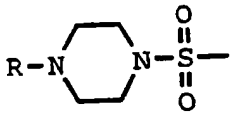
Accordingly, the present invention is a compound of Formula I

A-E-G-J

I

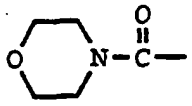
wherein A is

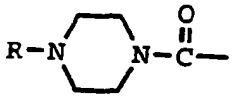




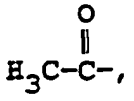
wherein R is hydrogen or alkyl of from one to six carbon atoms,

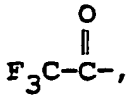
wherein R is as defined above,

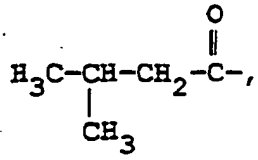


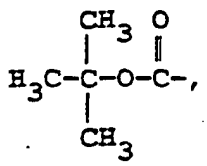


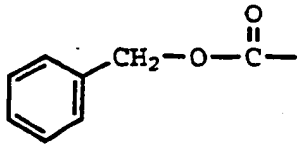
wherein R is as defined above,

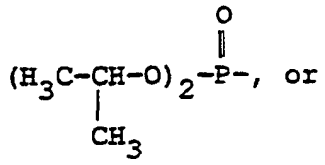




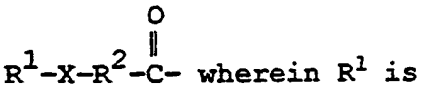






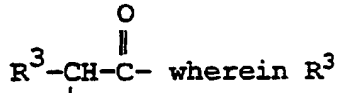


, or



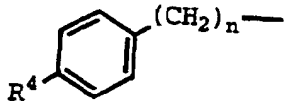
wherein $R^1$ is

hydrogen,



wherein $R^3$ is

hydrogen,

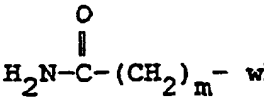


wherein n is zero or an integer of 1 or 2 and $R^4$ is hydrogen or hydroxyl,

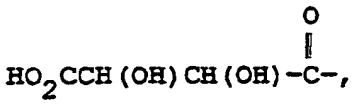
$CH_3-$,

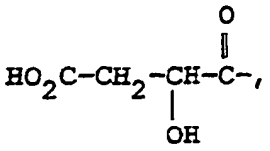
$H_2N-(CH_2)_4-$,

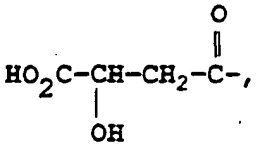
$HO_2C-(CH_2)_m-$ wherein m is an integer of 1 or 2, or

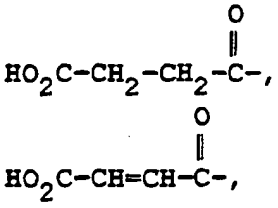


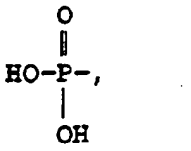
wherein m is as defined above,

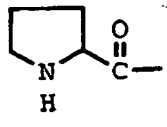












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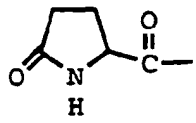
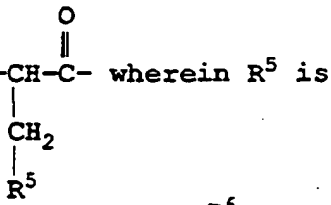
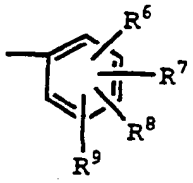


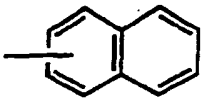
X is O, S, or NH, and

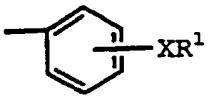
$R^2$ is alkyl of from one to six carbon atoms;

E is  wherein $R^5$ is

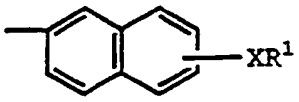


wherein $R^6$, $R^7$, $R^8$, or $R^9$ are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, halogen, or trifluoromethyl,

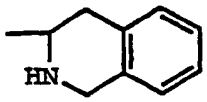


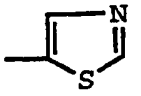


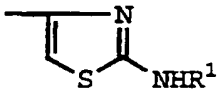

wherein $R^1$ and X are as defined above,



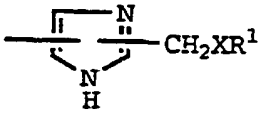

wherein $R^1$ and X are as defined above,



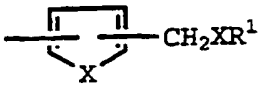



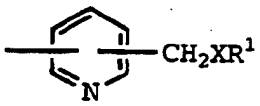

wherein $R^1$ is as defined above,

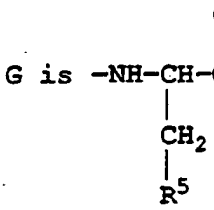


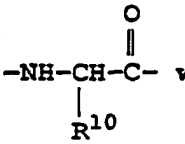

wherein X and $R^1$ are as defined above,




wherein $R^1$ and X are as defined above, or


wherein $R^1$ and X are as defined above;

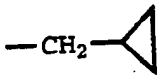
G is  wherein $R^5$ is as defined above, or


wherein $R^{10}$ is

hydrogen,

alkyl of from one to six carbon atoms,

$-CO_2CH_3$,

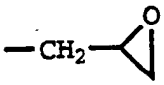


$-CH_2-CH=CH_2$,

$-CH_2-C\equiv CH$,

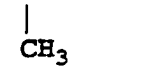
$-CH_2-CN$,

$-CH_2-OH$,



$-CH_2-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

$-CH_2X-R^1$ wherein X and $R^1$ are as defined above,



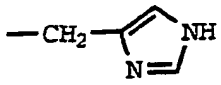
above,

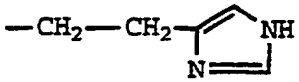
$-CH_2-CH_2CH_2CH_2-NH_2$,

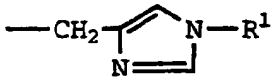
$-CH_2-CH_2-S(O)_n-R^1$ wherein n and $R^1$ are as

defined above,

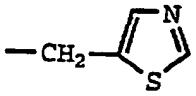
$-(CH_2)_n-CONH_2$ wherein n is as defined above,

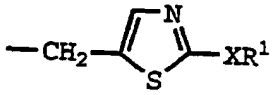






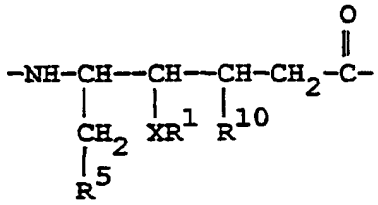
wherein $R^1$ is as defined above,

 , or

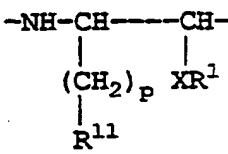


wherein X and $R^1$ are as defined above;

alternatively, E-G is

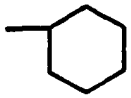


wherein $R^1$, X, $R^5$, and $R^{10}$ are as defined above;

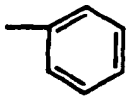
J is  wherein $R^{11}$ is

hydrogen,

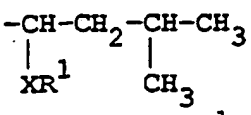
alkyl,



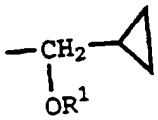
, or



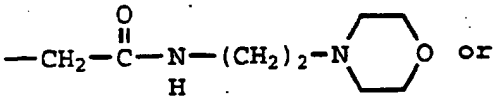
,

$R^{12}$ is 

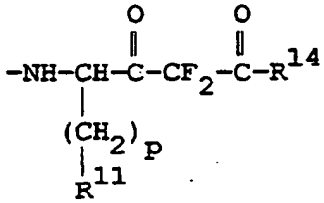
wherein $R^1$ and X are as defined above,



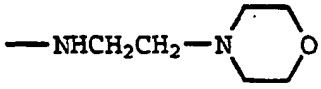
wherein $R^1$ and X are as defined above,



$-CH_2-OC_2H_5$ and $R^1$ and X are as defined above and p is zero or an integer of one, or



wherein $R^{14}$ is



or

$-OC_2H_5$

and $R^{11}$ and p are as defined above;

provided $R^1$ with the exclusion of $R^1$ being hydrogen is encompassed within the definition of at least one of A, E, G, or J; or a pharmaceutically acceptable salt thereof.

As amino acid prodrug renin inhibitors the compounds of Formula I are useful for the treatment of hypertension, hyperaldosteronism, congestive heart failure, and diseases caused by retroviruses including HTLC I, II, and III as well as diagnostic tools for the identification of cases of hypertension due to renin excess.

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of a compound of Formula I in unit dosage form in the treatment methods mentioned above.

Finally, the present invention is directed to methods for production of a compound of Formula I.

## DETAILED DESCRIPTION OF THE INVENTION

In the compounds of Formula I, the term "alkyl" means a straight or branched hydrocarbon radical having from one to six carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like.

"Alkoxy" is O-alkyl as defined above for alkyl.

"Halogen" is fluorine, chlorine, bromine, or iodine.

The following table provides a list of abbreviations and definitions thereof used in the present inventions.

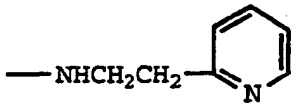
| Abbreviation* | Amino Acid |
|---|---|
| Ala | Alanine |
| Asp | Aspartic acid |

* If the optical activity of the amino acid is other than L(S), the amino acid or abbreviation is preceded by the appropriate configuration D(R) or DL(RS).

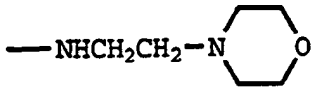
| Abbreviation | Amino Acid |
|---|---|
| Glu | Glutamic acid |
| Gln | Glutamine |
| Gly | Glycine |
| Lys | Lysine |
| Phe | Phenylalanine |
| Pro | Proline |
| Ser | Serine |
| Thr | Threonine |
| Tyr | Tyrosine |

| Abbreviation | Modified and Unusual Amino Acid |
|---|---|
| Alg | 2-Amino-4-pentenoic acid (Allylglycine) |
| Atm | 2-Amino-3-(2-amino-5-thiazole)propanoic acid |
| Chx | Cyclohexylalanine (Hexahydrophenylalanine) |
| Hse | 2-Amino-4-hydroxybutyric acid (Homoserine) |
| Mal | 2-Amino-1,3-propanedioic acid, monomethyl ester |
| Pgy | 2-Aminopentanoic acid (Propylglycine) |

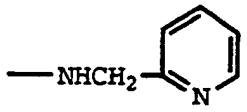
Amides With



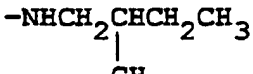
2-(2-Aminoethyl)pyridine



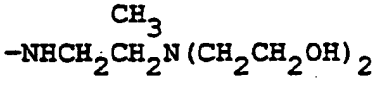
N-(2-Aminoethyl)morpholine



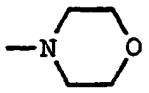
2-Aminomethylpyridine



2-Methylbutylamine



2-Bis(2-hydroxyethyl)-amino)ethylamine

| Abbreviation | Esters With |
|---|---|
|  | Morpholine |
| $-OCH_3$ | Methanol |
| $-OC_2H_5$ | Ethanol |
| $-OCH(CH_3)_2$ | 2-Propanol |
| $-OC(CH_3)_3$ | tertiary Butanol |
| -OBz | Benzyl alcohol |
| | **Protecting Group** |
| Cbz | Benzyloxycarbonyl |
| Boc | tertiary Butyloxycarbonyl |
| TBDMS | tertiary Butyldimethylsilyl |
| | **Miscellaneous** |
| CAD | 2(S)-Amino-1-cyclohexyl-6-methyl-3(R),4(S)-heptanediol |
| SMO | N-Morpholinesulphonyl |
| Ph | Phenyl |
| Bz | Benzyl |
| **Abbreviation** | **Solvents and Reagents** |
| DMF | N,N-Dimethylformamide |
| DMAP | 4-Dimethylamino pyridine |
| DMSO | Dimethylsulfoxide |
| HOBT | Hydroxybenzotriazole |
| DCC | N,N'-Dicyclohexyl-carbodiimide |
| DCU | 1,3-Dicyclohexylurea |
| HOAc | Acetic acid |
| $Et_3N$ | Triethylamine |
| THF | Tetrahydrofuran |
| $CH_2Cl_2$ | Dichloromethane |
| $CHCl_3$ | Chloroform |
| $Et_2O$ | Diethyl ether |
| CDI | Carbonyl Diimidazole |
| TBAF | Tetra-n-butylammonium fluoride |
| $KBH_4$ | Potassium Borohydride |
| DMAP | N,N-Dimethylaminopyridine |
| EtOAc | Ethyl Acetate |
| NaCl | Sodium Chloride |

| Abbreviation | Solvents and Reagents |
|---|---|
| $Na_2SO_3$ | Sodium Sulfite |
| $NaHCO_3$ | Sodium Bicarbonate |
| $NaIO_4$ | Sodium periodate |
| $Na_2CO_3$ | Sodium Carbonate |
| $MgSO_4$ | Magnesium Sulfate |
| HCl | Hydrochloric acid |
| EtOH | Ethanol |
| MeOH | Methanol |
| $D_2O$ | Deuterium Oxide |
| $Na_2SO_4$ | Sodium Sulfate |
| TFA | Trifluoroacetic acid |
| TsOH | Para-toluenesulfonic acid |

An amino acid or organic acid within the bracket in a structure means the bracketed moiety is attached via the α carboxylic acid or carboxylic acid, respectively, to the free hydroxyl or phenolic group of the preceding amino acid or organic alcohol (where there is more than one free hydroxyl or phenolic group in the preceding moiety the amino acid or organic acid may be attached to either or both) to form an ester such as, for example:

Ser(Phe),
Ser(Gln),
Ser(Pro),
Ser(Glu),
Ser(Lys),
Ser(Asp),
Ser(Gly),
Ser(Ala),
Ser($COCH_2CH_2CO_2H$),
Ser($P(O)(OH)_2$),
Ser($COCH(OH)CH(OH)CO_2H$),
Thr(Phe),
Thr(Gln),
Thr(Pro),
Thr(Glu),
Thr(Lys),

Thr(Asp),
Thr(Gly),
Thr(Ala),
Thr($COCH_2CH_2CO_2H$),
Thr($P(O)(OH)_2$),
Thr($COCH(OH)CH(OH)CO_2H$),
Tyr(Phe),
Tyr(Gln),
Tyr(Pro),
Tyr(Glu),
Tyr(Lys),
Tyr(Asp),
Tyr(Gly),
Tyr(Ala),
Tyr($COCH_2CH_2CO_2H$),
Tyr($P(O)(OH)_2$),
Tyr($COCH(OH)CH(OH)CO_2H$),
Hse(Phe),
Hse(Gln),
Hse(Pro),
Hse(Glu),
Hse(Lys),
Hse(Asp),
Hse(Gly),
Hse(Ala),
Hse($COCH_2CH_2CO_2H$),
Hse($P(O)(OH)_2$),
Hse($COCH(OH)CH(OH)CO_2H$),
CAD(Phe),
CAD(Gln),
CAD(Pro),
CAD(Glu),
CAD(Lys),
CAD(Asp),
CAD(Gly),
CAD(Ala),
CAD($COCH_2CH_2CO_2H$),

CAD($P(O)(OH)_2$),

CAD($COCH(OH)CH(OH)CO_2H$),

CAD(2·Phe),

CAD(2·Gln),

CAD(2·Pro),

CAD(2·Glu),

CAD(2·Lys),

CAD(2·Asp),

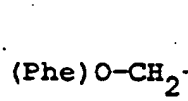
CAD(2·Gly),

CAD(2·Ala),

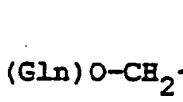
CAD($2\cdot COCH_2CH_2CO_2H$),

CAD($2\cdot P(O)(OH)_2$),

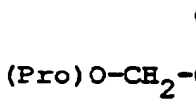
CAD($2\cdot COCH(OH)CH(OH)CO_2H$),



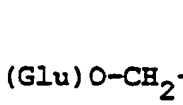
(Phe)O-$CH_2$-C-,



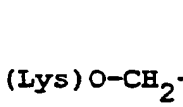
(Gln)O-$CH_2$-C-,



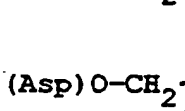
(Pro)O-$CH_2$-C-,



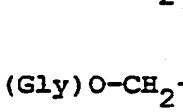
(Glu)O-$CH_2$-C-,



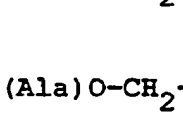
(Lys)O-$CH_2$-C-,



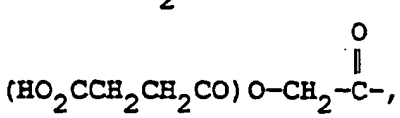
(Asp)O-$CH_2$-C-,



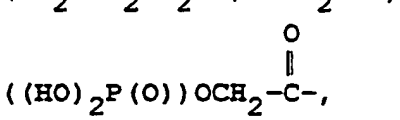
(Gly)O-$CH_2$-C-,



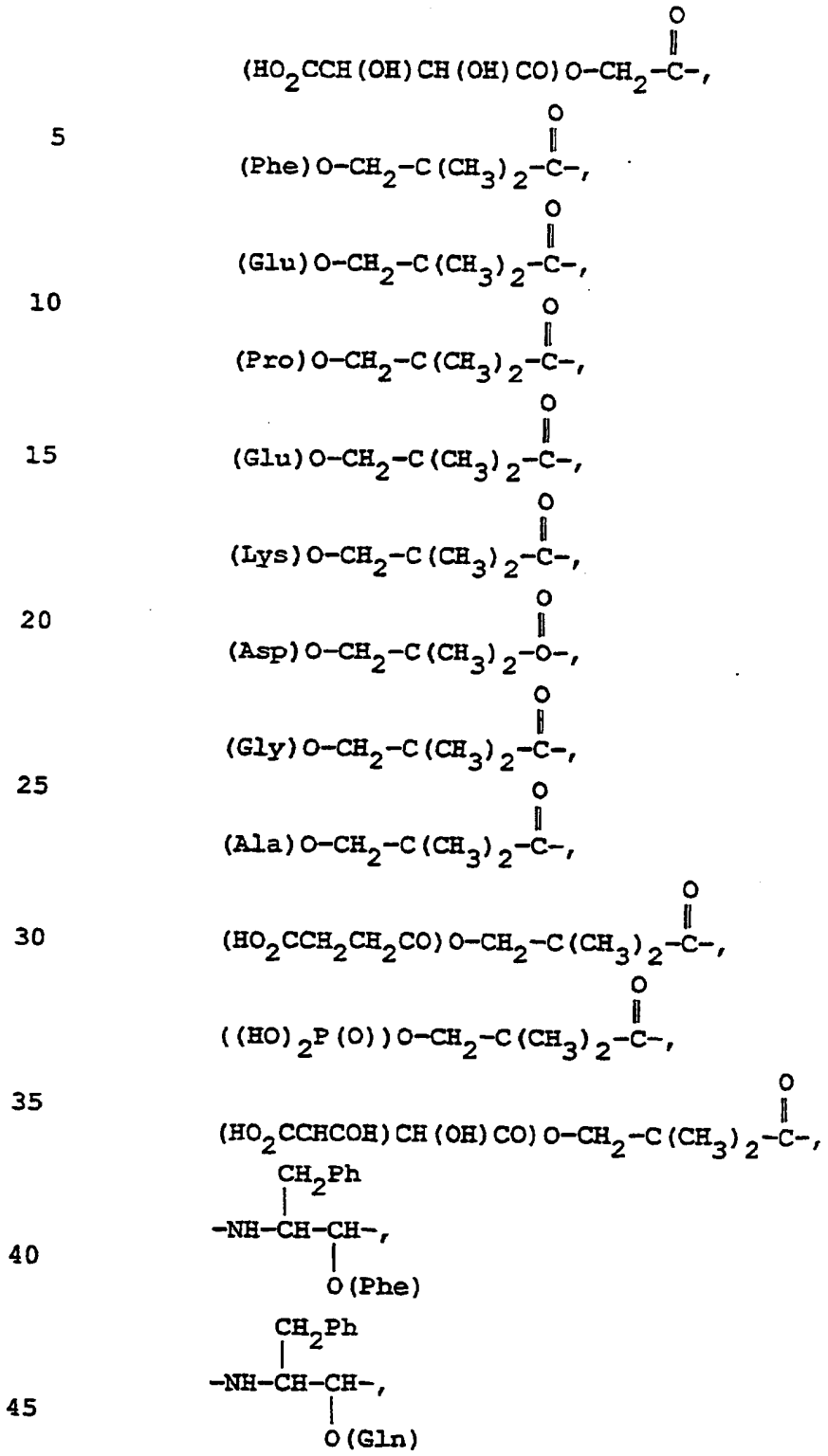
(Ala)O-$CH_2$-C-,

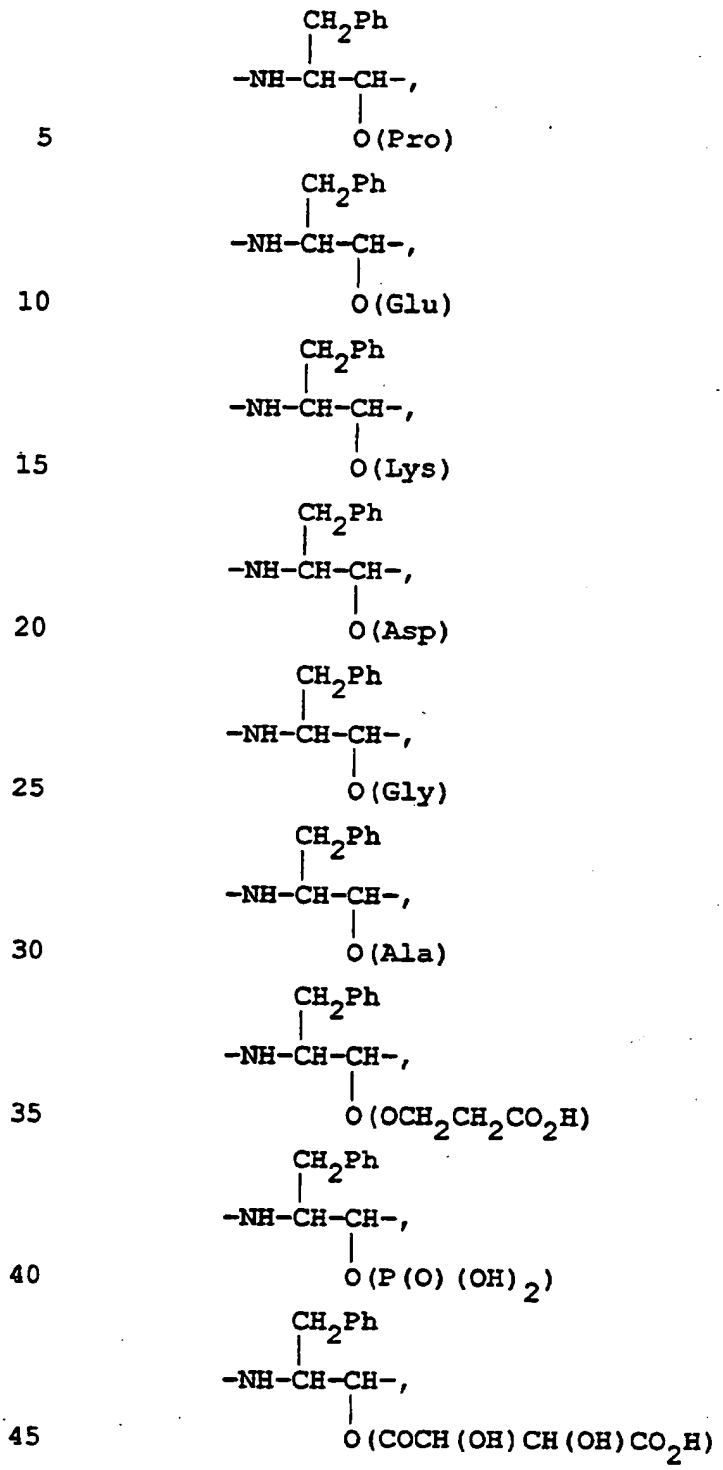


($HO_2CCH_2CH_2CO$)O-$CH_2$-C-,



($(HO)_2P(O)$)$OCH_2$-C-,




CH2Ph
-NH-CH-CH-,
O(Pro)
CH2Ph
-NH-CH-CH-,
O(Glu)
CH2Ph
-NH-CH-CH-,
O(Lys)
CH2Ph
-NH-CH-CH-,
O(Asp)
CH2Ph
-NH-CH-CH-,
O(Gly)
CH2Ph
-NH-CH-CH-,
O(Ala)
CH2Ph
-NH-CH-CH-,
O(OCH2CH2CO2H)
CH2Ph
-NH-CH-CH-,
O(P(O)(OH)2)
CH2Ph
-NH-CH-CH-,
O(COCH(OH)CH(OH)CO2H)

However, when the preceding unbracketed moiety is an organic amine, the bracketed amino acid or organic acid forms an amide bond with the amine such as, for example:

Atm(Phe),
Atm(Gln),
Atm(Pro),
Atm(Glu),
Atm(Lys),
Atm(Asp),
Atm(Gly),
Atm(Ala),
$Atm(COCH_2CH_2CO_2H)$,
$Atm(P(O)(OH)_2)$,
$Atm(COCH(OH)CH(OH)CO_2H)$,

For purposes of the present invention a "prodrug" refers to a compound of Formula I which is biotransformed into the active renin inhibitor in a mammal.

The compounds of Formula I are capable of further forming pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compound of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous and the like, as well as the salts derived from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate,

chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Bergs S. M., et al, "Pharmaceutical Salts," Journal of Pharmaceutical Science, Vol. 66, pages 1-19 (1977)).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free bases for purposes of the present invention.

Pharmaceutically acceptable base addition salts of acidic compounds are formed with metals or amines such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S. M., et al, Journal of Pharmaceutical Science, Vol. 66, pages 1-19 (1977)).

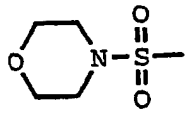
The base addition salts of said acidic compounds are prepared by contacting the free acid form with a

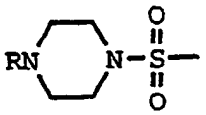
sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acids for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

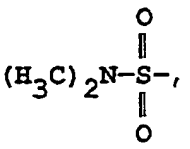
The compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric forms as well as the appropriate mixtures thereof.

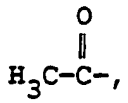
A preferred compound of Formula I is one wherein A is

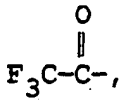


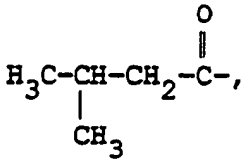


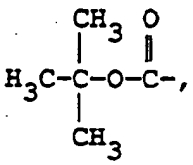
wherein R is hydrogen or alkyl of from one to six carbon atoms,

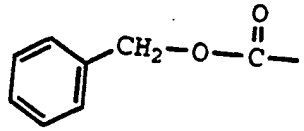


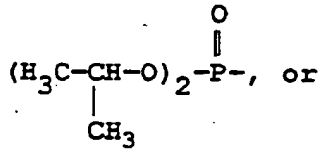




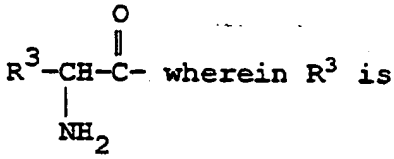




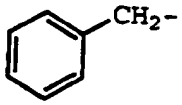




$R^1-O-R^2-C-$ wherein $R^1$ is



hydrogen,

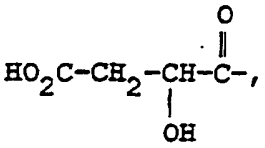


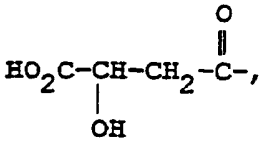
$CH_3-$,

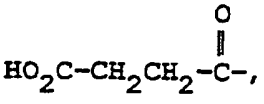
$H_2N-(CH_2)_4-$,

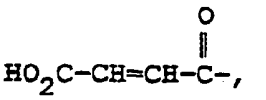
$HO_2C-(CH_2)_m-$ wherein m is an integer of 1 of 2, or

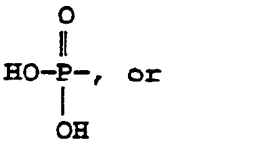

$H_2N-C-(CH_2)_m-$ wherein m is as defined above,

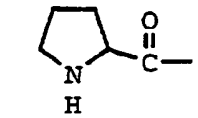




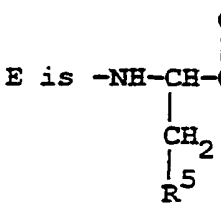


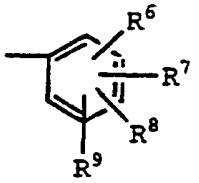




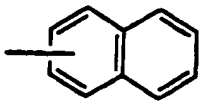

and

$R^2$ is alkyl of from one to six carbon atoms;

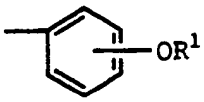

E is $-NH-CH(CH_2R^5)-C-$ wherein $R^5$ is


wherein $R^6$, $R^7$, $R^8$, or $R^9$ are each independently hydrogen,

alkyl of from one to six carbon atoms, alkoxyl of from one to six carbon atoms, halogen or trifluoromethyl,



or

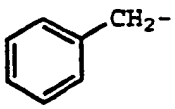


wherein $R^1$ is

hydrogen,

$R^3-CH(NH_2)-C(=O)-$ wherein $R^3$ is

hydrogen,



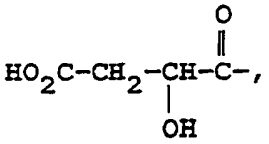
$CH_3-$,

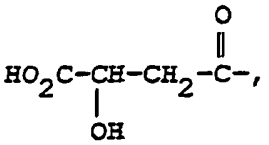
$H_2N-(CH_2)_4-$,

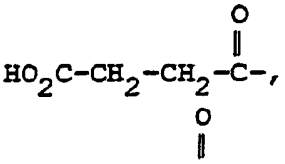
$HO_2C-(CH_2)_m-$ wherein m is an integer of 1 or 2, or

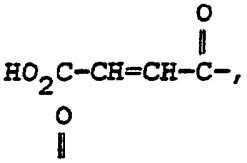
$H_2N-C(=O)-(CH_2)_m-$ wherein m is as defined above,

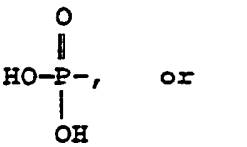
$HO_2C-CH(OH)CH(OH)-C(=O)-$,

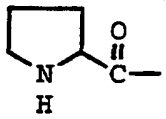




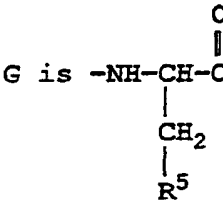


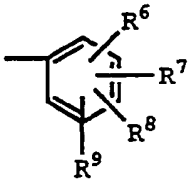




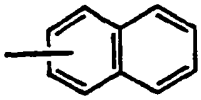


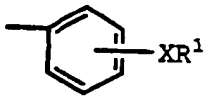
;

G is  wherein $R^5$ is

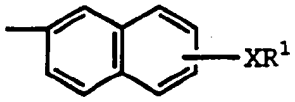


wherein $R^6$, $R^7$, $R^8$, or $R^9$ are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, halogen, or trifluoromethyl,

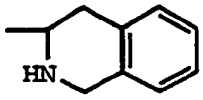


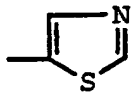


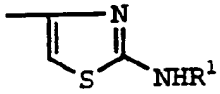
wherein X is O, S, or NH and $R^1$ is as defined above



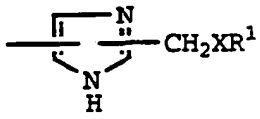
wherein $R^1$ and X are as defined above,



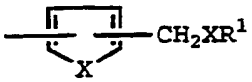


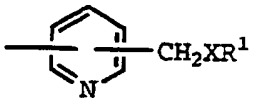


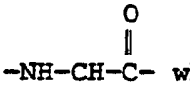
wherein $R^1$ is as defined above,



wherein X and $R^1$ are as defined above,


wherein $R^1$ and X are as defined above,

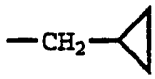

wherein $R^1$ and X are as defined above, or


wherein $R^{10}$ is

hydrogen,

alkyl of from one to six carbon atoms,

$-CO_2CH_3$,

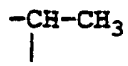


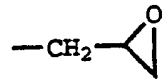
$-CH_2-CH=CH_2$,

$-CH_2-C\equiv CH$,

$-CH_2-CN$,

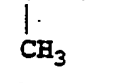
$-CH_2-OH$,





$-CH_2-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

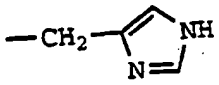
$-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

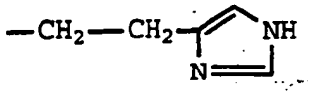

wherein X and $R^1$ are as defined above,

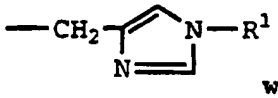
$-CH_2-CH_2CH_2CH_2-NH_2$,

$-CH_2-CH_2-S(O)_n-R^1$ wherein n is zero or an integer of 1 or 2 and $R^1$ is as defined above,

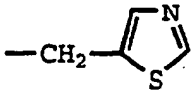
$-(CH_2)_n-CONH_2$ wherein n is as defined above,



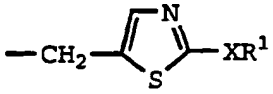




wherein $R^1$ is as defined above,

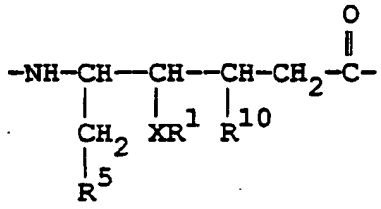


, or

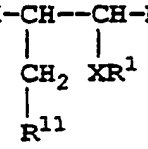


wherein X and $R^1$ are as defined above;

alternatively, E-G is

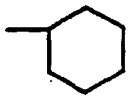


wherein $R^1$, X, $R^5$, and $R^{10}$ are as defined above;

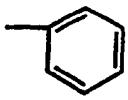
J is  wherein $R^{11}$ is

hydrogen,

alkyl,

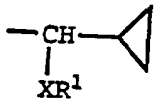


, or

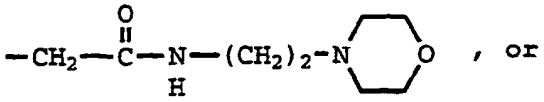


,

$R^{12}$ is $-CH(OR^1)-CH_2-CH(CH_3)-CH_3$ wherein $R^1$ is as defined above,



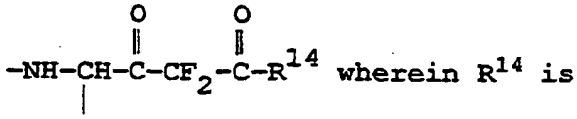
wherein $R^1$ is as defined above,



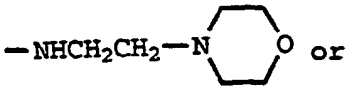
, or

$-CH_2-OC_2H_5$ and $R^1$ and X are as defined above

or



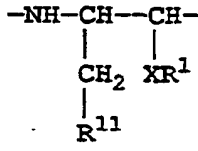
wherein $R^{14}$ is



or

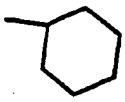
$-OC_2H_5$ and $R^{11}$ is as defined above; provided $R^1$ with the exclusion of $R^1$ being hydrogen is encompassed within the definition of at least one of A, E, G, or J.

A more preferred compound of Formula I is one wherein J is

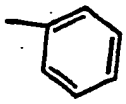


wherein $R^{11}$ is

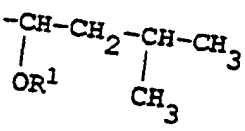
alkyl,

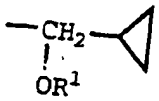


, or

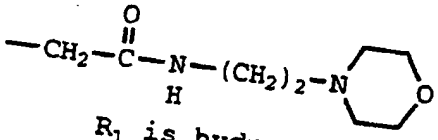


,

$R^{12}$ is 

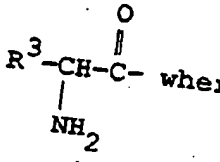


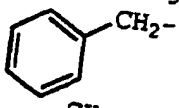
or



and

$R_1$ is hydrogen,

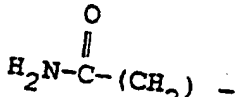
 wherein $R^3$ is hydrogen,

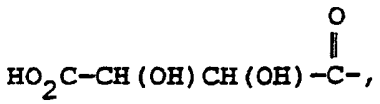


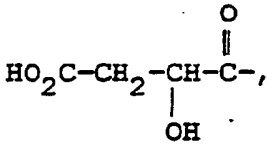
$CH_3$-,

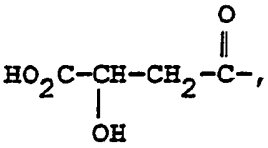
$H_2N-(CH_2)_4$-,

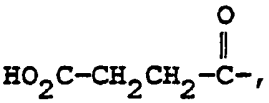
$HO_2C-(CH_2)_m$- wherein m is an integer of 1 or 2, or

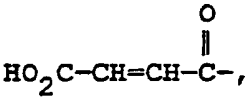
 wherein m is as defined above,

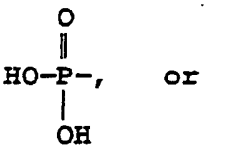


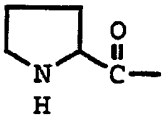




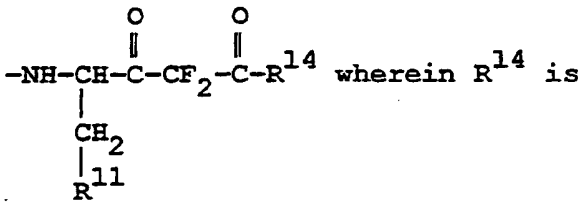




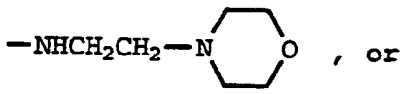




and X is O, S, or NH, or



wherein $R^{14}$ is



, or

$-OC_2H_5$ and

$R^{11}$ is as defined above.

Particularly valuable are:

SMO-Phe-Ser(Phe)-CAD;

SMO-Phe-Ser(Gln)-CAD;

SMO-Phe-Ser(Pro)-CAD;

SMO-Phe-Ser(Glu)-CAD;
SMO-Phe-Ser(Lys)-CAD;
SMO-Phe-Ser(Asp)-CAD;
SMO-Phe-Ser(Gly)-CAD;
SMO-Phe-Ser(Ala)-CAD;
SMO-Phe-Ser($COCH_2CH_2CO_2H$)-CAD;
SMO-Phe-Ser(P(O)$(OH)_2$)-CAD;
SMO-Phe-Ser(COCH(OH)CH(OH)$CO_2H$)-CAD;
SMO-Phe-Thr(Phe)-CAD;
SMO-Phe-Thr(Gln)-CAD;
SMO-Phe-Thr(Pro)-CAD;
SMO-Phe-Thr(Glu)-CAD;
SMO-Phe-Thr(Lys)-CAD;
SMO-Phe-Thr(Asp)-CAD;
SMO-Phe-Thr(Gly)-CAD;
SMO-Phe-Thr(Ala)-CAD;
SMO-Phe-Thr($COCH_2CH_2CO_2H$)-CAD;
SMO-Phe-Thr(P(O)$(OH)_2$)-CAD;
SMO-Phe-Thr(COCH(OH)CH(OH)$CO_2H$)-CAD;
Boc-Tyr(Phe)-Pgy-CAD;
Boc-Tyr(Gln)-Pgy-CAD;
Boc-Tyr(Pro)-Pgy-CAD;
Boc-Tyr(Glu)-Pgy-CAD;
Boc-Tyr(Lys)-Pgy-CAD;
Boc-Tyr(Asp)-Pgy-CAD;
Boc-Tyr(Gly)-Pgy-CAD;
Boc-Tyr(Ala)-Pgy-CAD;
Boc-Tyr($COCH_2CH_2CO_2H$)-Pgy-CAD;
Boc-Tyr(P(O)(OH)CH(OH)$CO_2H$)-Pgy-CAD;
Boc-Tyr(COCH(OH)CH(OH)$CO_2H$)-Pgy-CAD;
SMO-Phe-Hse(Phe)-CAD;
SMO-Phe-Hse(Gln)-CAD;
SMO-Phe-Hse(Pro)-CAD;
SMO-Phe-Hse(Glu)-CAD;
SMO-Phe-Hse(Lys)-CAD;
SMO-Phe-Hse(Asp)-CAD;
SMO-Phe-Hse(Gly)-CAD;

SMO-Phe-Hse(Ala)-CAD;

SMO-Phe-Hse($COCH_2CH_2CO_2H$)-CAD;

SMO-Phe-Hse($P(O)(OH)_2$)-CAD;

SMO-Phe-Hse($COCH(OH)CH(OH)CO_2H$)-CAD;

SMO-Phe-Mal-CAD(2·Phe);

SMO-Phe-Mal-CAD(2·Gln);

SMO-Phe-Mal-CAD(2·Pro);

SMO-Phe-Mal-CAD(2·Glu);

SMO-Phe-Mal-CAD(2·Lys);

SMO-Phe-Mal-CAD(2·Asp);

SMO-Phe-Mal-CAD(2·Gly);

SMO-Phe-Mal-CAD(2·Ala);

SMO-Phe-Mal-CAD(2·$COCH(OH)CH(OH)CO_2H$);

SMO-Phe-Mal-CAD(2·$P(O)(OH)_2$);

SMO-Phe-Mal-CAD(2·$COCH(OH)CH(OH)CO_2H$);

SMO-Phe-Atm-CAD(2·Phe);

SMO-Phe-Atm-CAD(2·Gln);

SMO-Phe-Atm-CAD(2·Pro);

SMO-Phe-Atm-CAD(2·Glu);

SMO-Phe-Atm-CAD(2·Lys);

SMO-Phe-Atm-CAD(2·Asp);

SMO-Phe-Atm-CAD(2·Gly);

SMO-Phe-Atm-CAD(2·Ala);

SMO-Phe-Atm-CAD(2·$COCH_2CH_2CO_2H$);

SMO-Phe-Atm-CAD(2·$P(O)(OH)_2$);

SMO-Phe-Atm-CAD(2·$COCH(OH)CH(OH)CO_2H$);

SMO-Phe-Atm(Phe)-CAD;

SMO-Phe-Atm(Gln)-CAD;

SMO-Phe-Atm(Pro)-CAD;

SMO-Phe-Atm(Glu)-CAD;

SMO-Phe-Atm(Lys)-CAD;

SMO-Phe-Atm(Asp)-CAD;

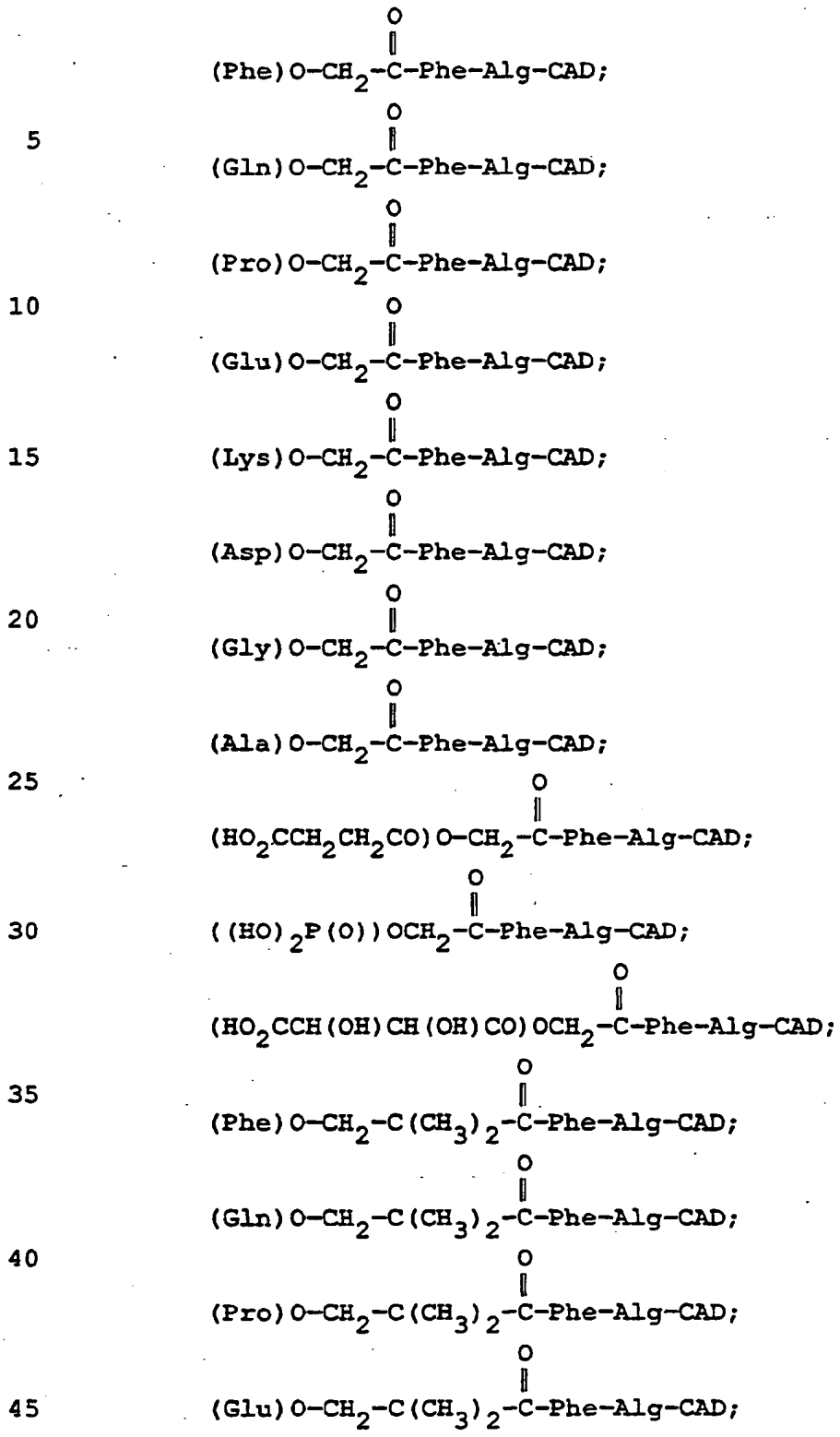
SMO-Phe-Atm(Gly)-CAD;

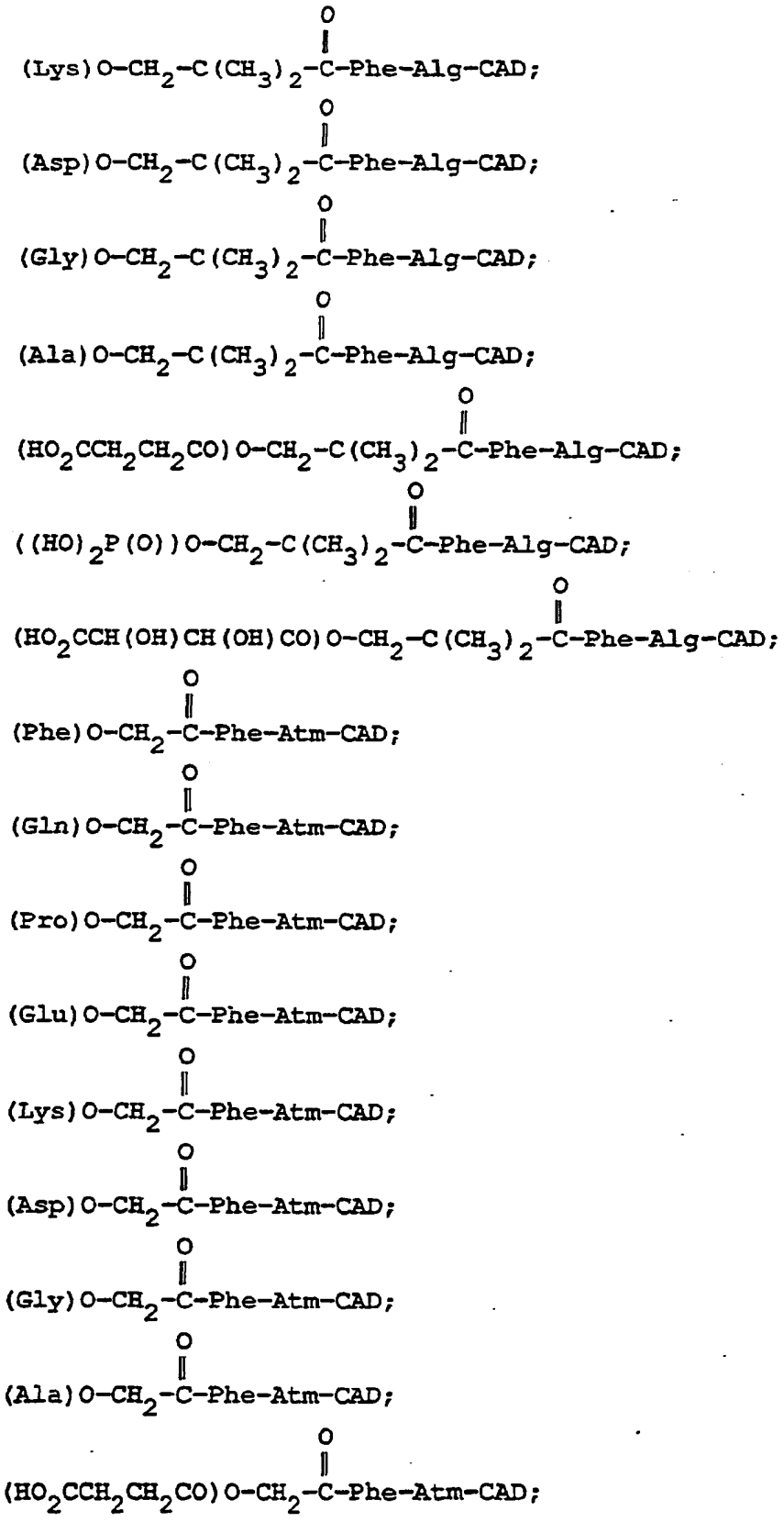
SMO-Phe-Atm(Ala)-CAD;

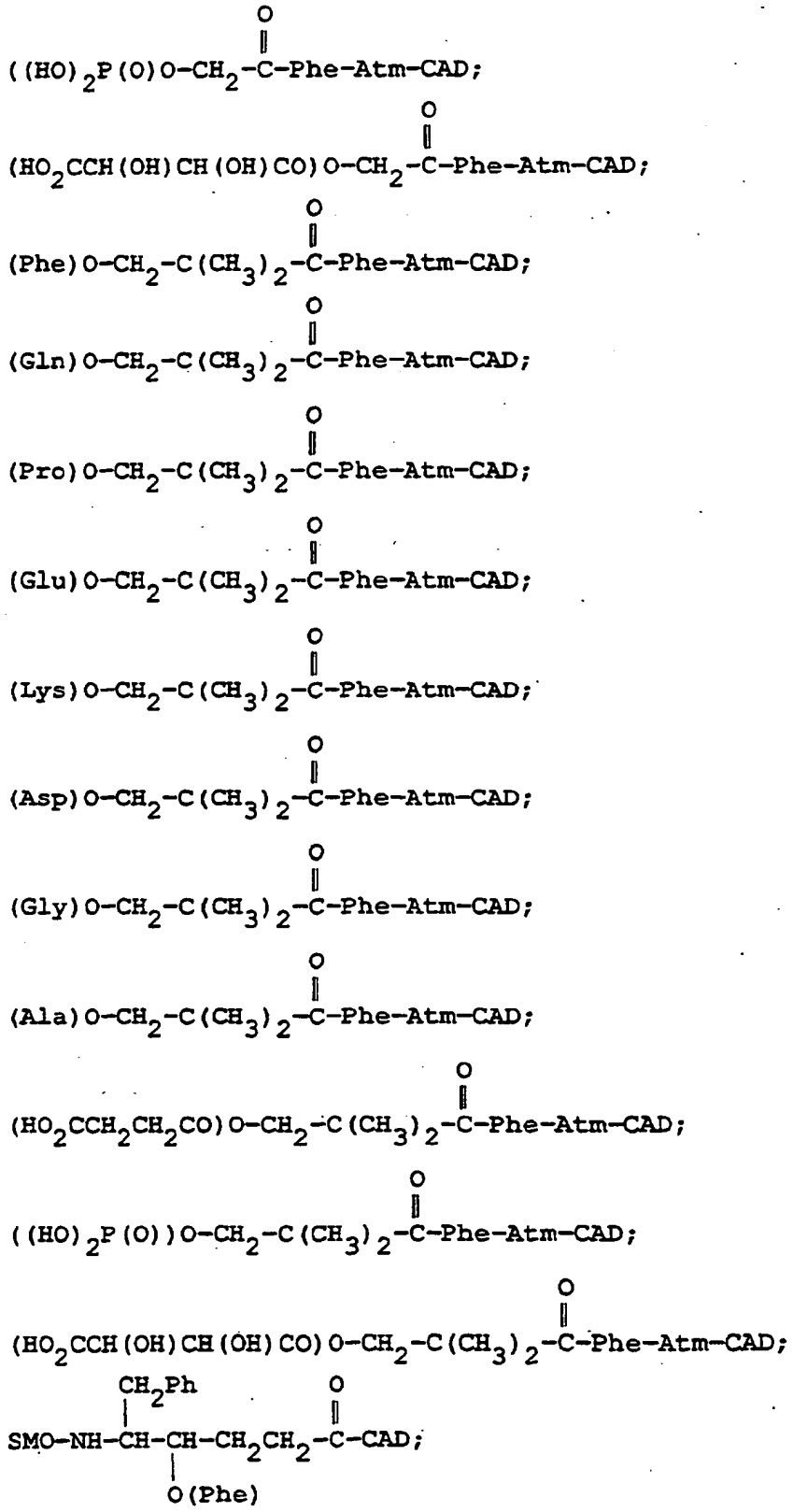
SMO-Phe-Atm($COCH_2CH_2CO_2H$)-CAD;

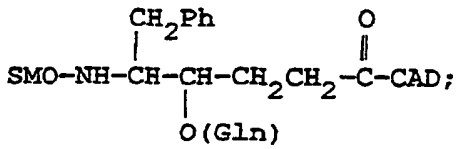
SMO-Phe-Atm($P(O)(OH)_2$)-CAD;

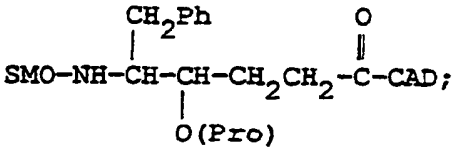
SMO-Phe-Atm($COCH(OH)CH(OH)CO_2H$)-CAD;

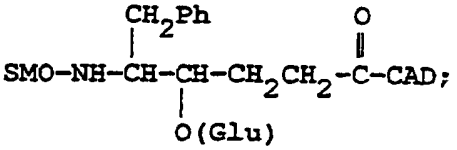

(Phe)O-CH2-C-Phe-Alg-CAD;
(Gln)O-CH2-C-Phe-Alg-CAD;
(Pro)O-CH2-C-Phe-Alg-CAD;
(Glu)O-CH2-C-Phe-Alg-CAD;
(Lys)O-CH2-C-Phe-Alg-CAD;
(Asp)O-CH2-C-Phe-Alg-CAD;
(Gly)O-CH2-C-Phe-Alg-CAD;
(Ala)O-CH2-C-Phe-Alg-CAD;
(HO2CCH2CH2CO)O-CH2-C-Phe-Alg-CAD;
((HO)2P(O))OCH2-C-Phe-Alg-CAD;
(HO2CCH(OH)CH(OH)CO)OCH2-C-Phe-Alg-CAD;
(Phe)O-CH2-C(CH3)2-C-Phe-Alg-CAD;
(Gln)O-CH2-C(CH3)2-C-Phe-Alg-CAD;
(Pro)O-CH2-C(CH3)2-C-Phe-Alg-CAD;
(Glu)O-CH2-C(CH3)2-C-Phe-Alg-CAD;

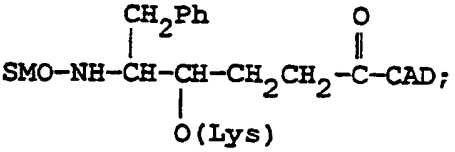


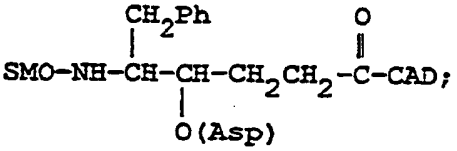


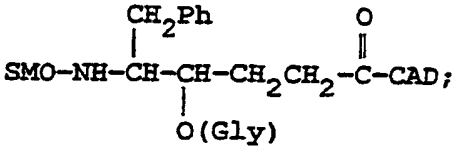


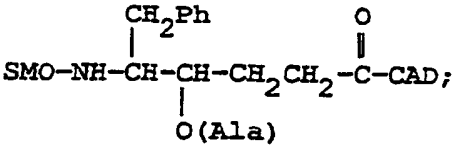


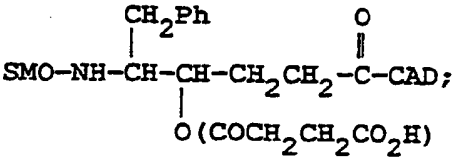


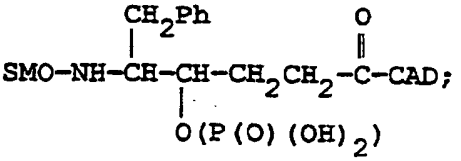


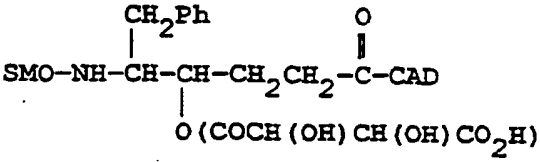














BNSDOCID <WO__9306127A1_I_>

or a pharmaceutically acceptable salt thereof.

Amidon, G.L., et al, Journal of Pharmaceutical Sciences, Vol. 69, pages 1363-1368 (1980) described a procedure for improving the intestinal absorption of water - insoluble drugs. This strategy converts the insoluble compound to a soluble derivative which subsequently is converted enzymatically to the parent compound in vivo. Thus, the soluble derivatives of the water insoluble drug acts as a prodrug which is converted by enzymes in the surface coat of the brush border region of the microvillous membrane in the intestine to the desired drug. The ability of a compound of Formula I which is a water soluble amino acid derivative of a renin inhibitor to act as a prodrug that is converted by intestinal enzymes to the parent renin inhibitor is tested using the following procedure.

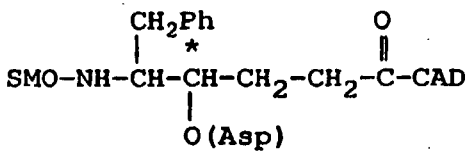
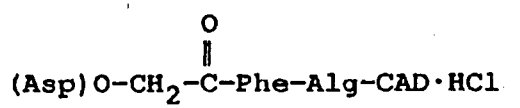
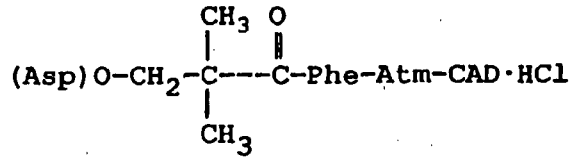
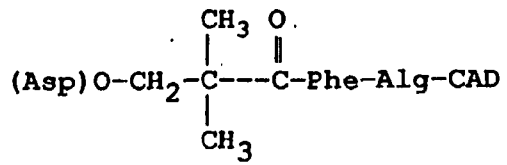
Stability in Intestinal Perfusate - Perfusate is generated by oscillating 15 to 20 mL MES buffer through rat jejunum in situ at 30 mL/min using a withdrawal/infusion pump (Harvard Apparatus, Model 4200-015). At 1.5 h, the perfusate is collected and spiked with prodrug at 37 µg/mL. The solution is incubated at 37°C and disappearance of prodrug over time is monitored by direct injection (25 µL) onto HPLC.

Stability in Suspensions of Brush Border Membranes (BBM) - BBM are prepared from rat or rabbit small intestine by the method of Kessler, et al, Biochim. Biophys. Acta 506:136-154, (1978) with some modifications. Vesicles (50 µL) are combined with 450 µL drug or prodrug (10 µg/mL) and incubated at 37°C. At selected time points, 100 µL prodrug/BBM suspension is removed and diluted with 100 µL acetonitrile, then 150 µL MES, centrifuged, and 50 µL is injected onto HPLC.

HPLC Conditions - Samples are analyzed by high pressure liquid chromatography using a two pump binary-gradient system (HP 1090 Liquid Chromatograph), a Lambda-Max LC Spectrophotometer (Waters, Model 481) set to 214 nm, and a ChromJet integrator (SpectraPhysics). The Econosil column (C8, 4.6 x 250 mm) is at room temperature. Solvent A is water/acetonitrile/triethylamine (TEA) (90:10:0.1) and solvent B is acetonitrile/water/TEA (70:30:0.1). The mobile phase is degassed and maintained with zero grade helium. Isocratic conditions consisted of 65% solvent A and 35% solvent B. At a flow rate of 1.0 mL/min, the retention times are 56 min for the drug and 9.6 min for the prodrug. MES buffer is 10 mM (2-[N-Morpholino]ethanesulfonic acid, made iso-osmotic with 10 mM KCl and 140 mM NaCl and adjusted to pH 6.5 with 1N NaOH.

The data in Table I show some representative water soluble amino acid prodrug renin inhibitors which are converted to the parent renin inhibitor by intestinal enzymes and also by brush border enzymes.

TABLE I

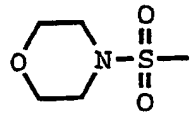
| Example | Compound | Perfusate t½ (minutes) | BBM t½ (minutes) | Selectivity (Perfusate t½/ BBM t½) |
|---|---|---|---|---|
| 1 | SMO-Phe-Ser(Lys·2HCl)-CAD | 36.4 | 36.9 | 0.99 |
| 2 | SMO-Phe-Ser(Asp·HCl)-CAD | 576.0 | 291.0 | 2.00 |
| 4 | SMO-Phe-Ser(Glu·TFA)-CAD | 388.0 | 235.0 | 1.70 |
| 5 | SMO-Phe-Ser(Gln·TFA)-CAD | 69.7 | 72.6 | 0.96 |
| 6 | SMO-Phe-Ser(Ala·TFA)-CAD | 50.2 | 54.1 | 0.93 |
| 9 |  (R-Isomer at *) | 100.4 h | 15.4 h | 6.67 |
| 11 |  | 32.4 | 4.7 | 7.00 |
| 12 |  | 508.5 | 14.0 | 36.32 |
| 13 |  | 197.0 | 11.7 | 17.00 |

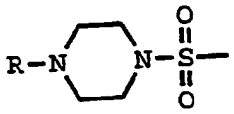
A method of preparing a compound having the Formula I

A-E-G-J

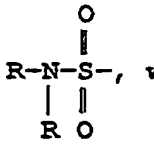
I

wherein A is

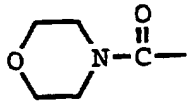


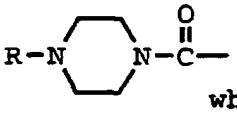


wherein R is hydrogen or alkyl of from one to six carbon atoms,

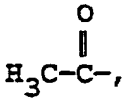


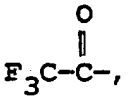
wherein R is as defined above,

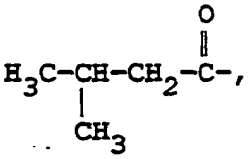


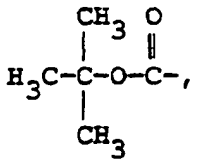


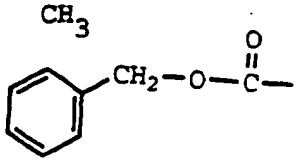
wherein R is as defined above,

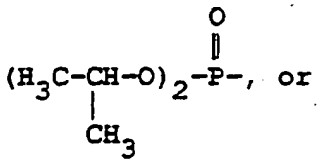




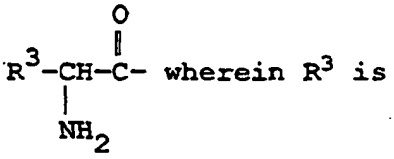




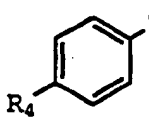




$R^1-X-R^2-\overset{O}{\overset{\|}{C}}-$ wherein $R^1$ is hydrogen,



wherein $R^3$ is hydrogen,

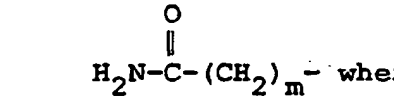


wherein n is zero or an integer of 1 or 2 and $R^4$ is hydrogen or hydroxyl,

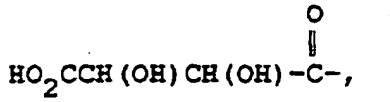
$CH_3-$,

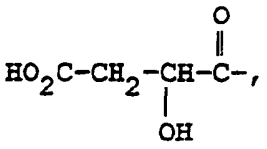
$H_2N-(CH_2)_4-$,

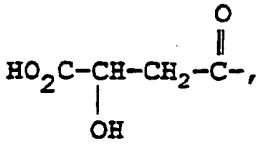
$HO_2C-(CH_2)_m-$ wherein m is an integer of 1 or 2, or

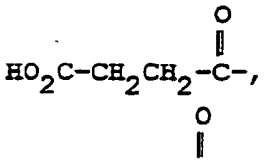


wherein m is as defined above,

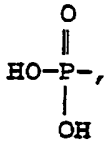


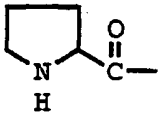




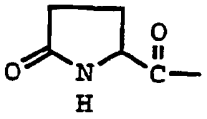






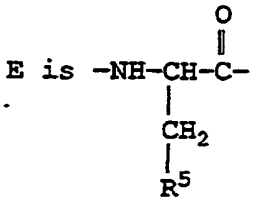


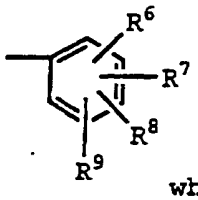
, or



X is O, S, or NH, and

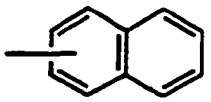
$R^2$ is alkyl of from one to six carbon atoms;

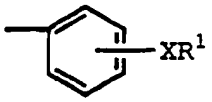
E is  wherein $R^5$ is



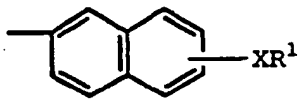
wherein $R^6$, $R^7$, $R^8$, or $R^9$ are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon

atoms, halogen, or trifluoromethyl,

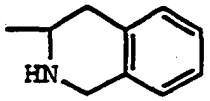
 ,




wherein $R^1$ and X are as defined above,




wherein $R^1$ and X are as defined above,



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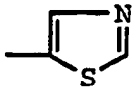

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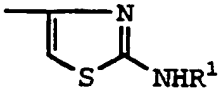
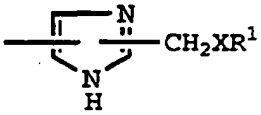
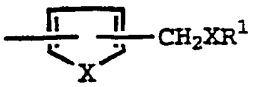
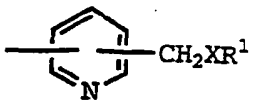


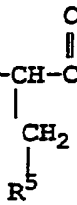

wherein $R^1$ is as defined above,

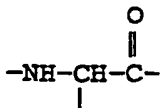



wherein X and $R^1$ are as defined above,


wherein $R^1$ and X are as defined above, or


wherein $R^1$ and X are as defined above;

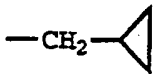
G is  wherein $R^5$ is as defined above, or


wherein $R^{10}$ is

hydrogen,

alkyl of from one to six carbon atoms,

$-CO_2CH_3$,

 ,

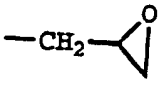
$-CH_2-CH=CH_2$,

$-CH_2-C\equiv CH$,

$-CH_2-CN$,

$-CH_2-OH$,

 ,

 ,

$-CH_2-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

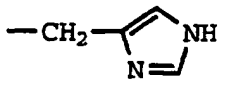
$-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

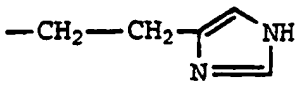
$-CHX-R^1$ wherein X and $R^1$ are as defined above,

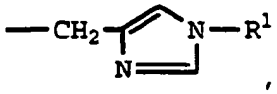
$-CH_2-CH_2CH_2CH_2-NH_2$,

$-CH_2-CH_2-S(O)_n-R^1$ wherein n and $R^1$ are as defined above,

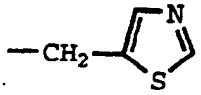
$-(CH_2)_n-CONH_2$ wherein n is as defined above,



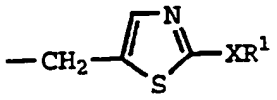




wherein $R^1$ is as defined above,

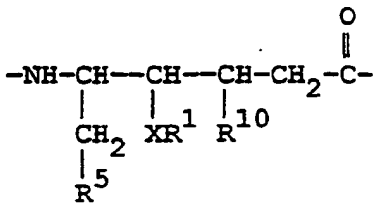


, or

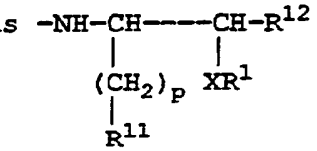


wherein X and $R^1$ are as defined above;

alternatively, E-G is

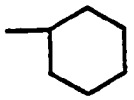


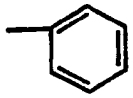
wherein $R^1$, X, $R^5$, and $R^{10}$ are as defined above;

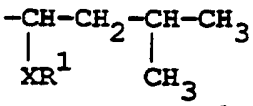
J is  wherein $R^{11}$ is

hydrogen,

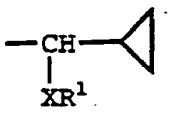
alkyl,

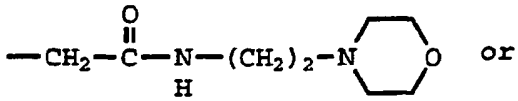
 , or

 ,

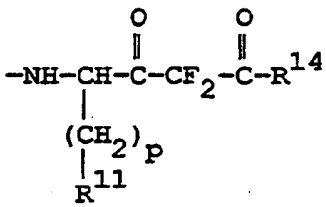
$R^{12}$ is 

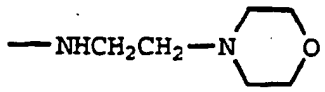
wherein $R^1$ and X are as defined above,

 wherein $R^1$ and X are as defined above,

 or

$-CH_2-OC_2H_5$ and $R^1$ and X are as defined above and p is zero or an integer of one, or

 wherein $R^{14}$ is



or

$-OC_2H_5$

and $R^{11}$ and p are as defined above;

provided $R^1$ with the exclusion of $R^1$ being hydrogen is encompassed within the definition of at least one of A, E, G, or J; or a pharmaceutically acceptable salt thereof comprises:

a) coupling a compound of Formula II

$$A'-E'-G'-J'$$

II

wherein A', E', G', and J' are as defined above for A, E, G, and J provided $R^1$ is hydrogen and is encompassed within the definition of at least one of A', E', G', or J' with a compound of Formula III

$$R^{1a}-XH$$

III

wherein $R^{1a}$ is as defined above for $R^1$ but excluding $R^1$ is hydrogen and providing any basic or acidic groups contain conventional protecting groups and X is as defined above to afford a compound of Formula IV

$$A''-E''-G''-J''$$

IV

wherein A'', E'', G'', and J'' are as defined above for A, E, G, and J provided $R^{1a}$ is as defined above and is encompassed within the definition of at least one of A'', E'', G'' or J'';

b) a compound of Formula IV is deprotected in a conventional manner to afford a compound of Formula I; and if desired, converting a compound of Formula I to a corresponding pharmaceutically acceptable salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable salt to a compound of Formula I by conventional means.

A compound of Formula II may be prepared by sequential stepwise or fragment coupling of the amino acids or fragments selected from A', E', G', or J' to the preceding amino acid or fragment using conventional peptide synthesis methodology such as, for example, solution peptide synthesis or solid phase peptide synthesis to afford a compound of Formula II.

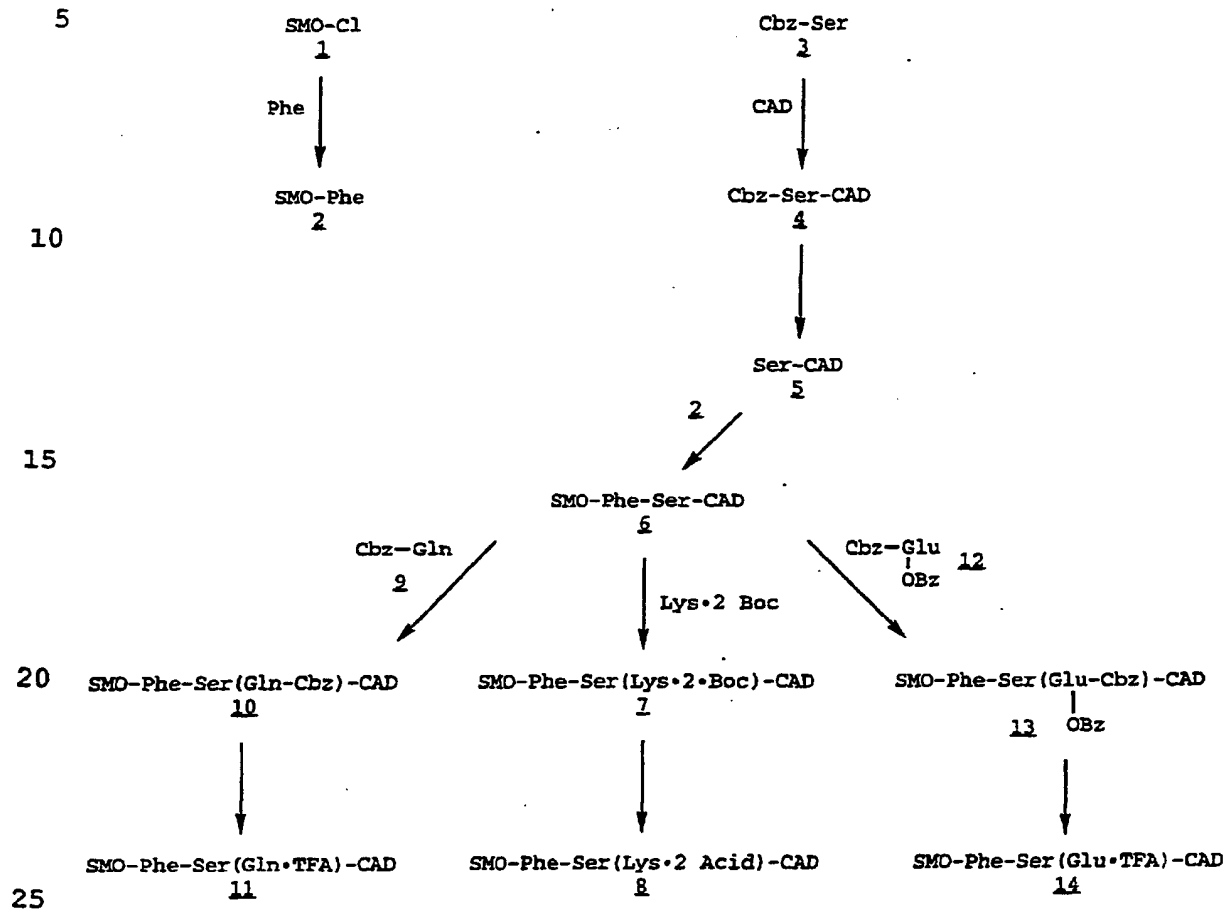
A compound of Formula IV is prepared from anino acids or fragments selected from A'', E'', G'', or J'' using the methodology used to prepare a compound of Formula II.

A compound of Formula III is either known or capable of being prepared by methods known in the art.

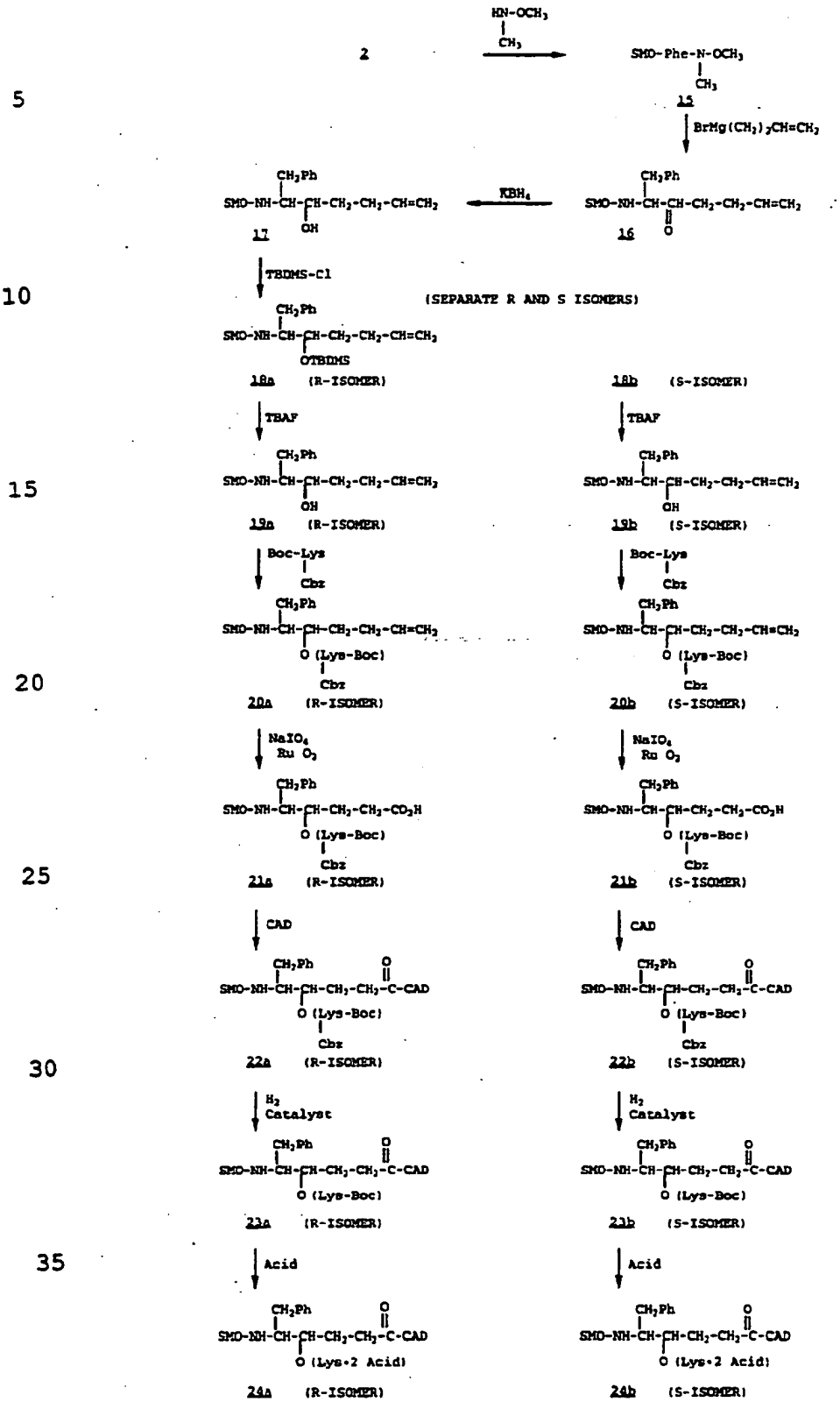
Coupling methods that can be employed in preparing the compounds of Formula I are discussed in "The Peptides. Analysis, Synthesis, Biology," Gross, E., and Meienhofer, J., eds. Academic Press, New York, New York, Vol. 1, 1979. Further, protecting groups that may be employed in the preparation of a compound of Formula I, as well as methods for incorporation and removal of these protecting groups are discussed in "The Peptides.

Analysis, Synthesis, Biology," Gross, E., and Meienhofer, J., eds., Academic Press, New York, New York, Vol. 3, 1981.

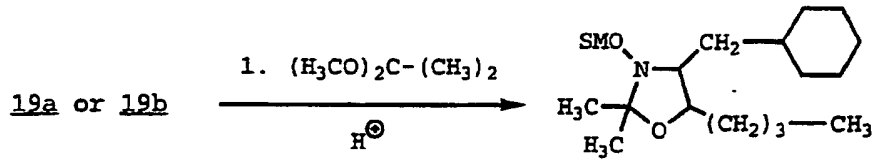
SCHEME 1


SMO-Cl
1
Phe
SMO-Phe
2
Cbz-Ser
3
CAD
Cbz-Ser-CAD
4
Ser-CAD
5
2
SMO-Phe-Ser-CAD
6
Cbz-Gln
9
Lys•2 Boc
Cbz-Glu
OBz
12
SMO-Phe-Ser(Gln-Cbz)-CAD
10
SMO-Phe-Ser(Lys•2•Boc)-CAD
7
SMO-Phe-Ser(Glu-Cbz)-CAD
13
OBz
SMO-Phe-Ser(Gln•TFA)-CAD
11
SMO-Phe-Ser(Lys•2 Acid)-CAD
8
SMO-Phe-Ser(Glu•TFA)-CAD
14

SCHEME 2

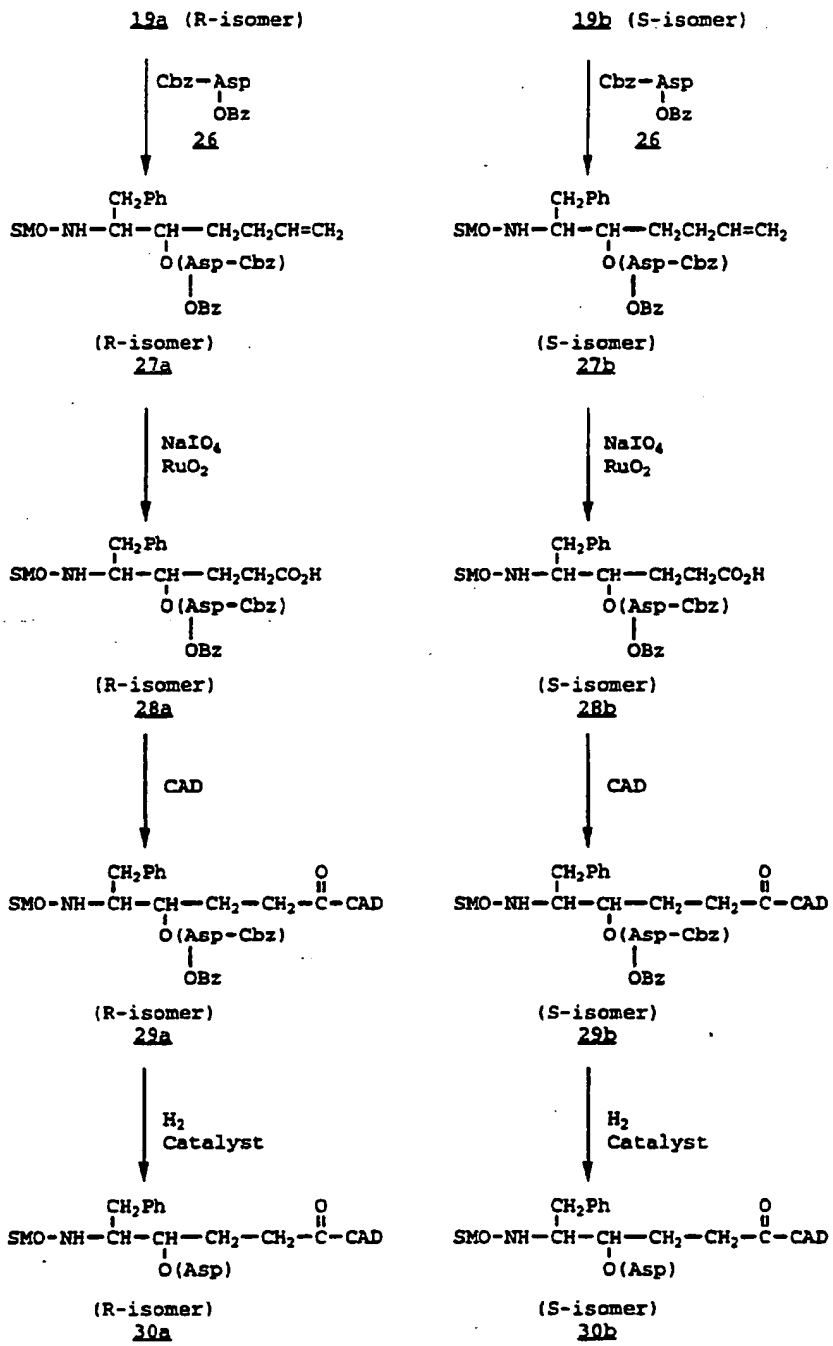

2
HN-OCH3
CH3
SMD-Phe-N-OCH3
CH3
15
BrMg(CH2)2CH=CH2
CH2Ph
SMD-NH-CH-CH-CH2-CH2-CH=CH2
OH
17
KBH4
CH2Ph
SMD-NH-CH-C-CH2-CH2-CH=CH2
O
16
TBDMS-Cl
(SEPARATE R AND S ISOMERS)
CH2Ph
SMD-NH-CH-CH-CH2-CH2-CH=CH2
OTBDMS
18a (R-ISOMER)
18b (S-ISOMER)
TBAF
CH2Ph
SMD-NH-CH-CH-CH2-CH2-CH=CH2
OH
19a (R-ISOMER)
19b (S-ISOMER)
Boc-Lys
Cbz
CH2Ph
SMD-NH-CH-CH-CH2-CH2-CH=CH2
O (Lys-Boc)
Cbz
20a (R-ISOMER)
20b (S-ISOMER)
NaIO4
Ru O2
CH2Ph
SMD-NH-CH-CH-CH2-CH2-CO2H
O (Lys-Boc)
Cbz
21a (R-ISOMER)
21b (S-ISOMER)
CAD
CH2Ph
SMD-NH-CH-CH-CH2-CH2-C-CAD
O (Lys-Boc)
Cbz
22a (R-ISOMER)
22b (S-ISOMER)
H2
Catalyst
CH2Ph
SMD-NH-CH-CH-CH2-CH2-C-CAD
O (Lys-Boc)
23a (R-ISOMER)
23b (S-ISOMER)
Acid
CH2Ph
SMD-NH-CH-CH-CH2-CH2-C-CAD
O (Lys•2 Acid)
24a (R-ISOMER)
24b (S-ISOMER)

SCHEME 3

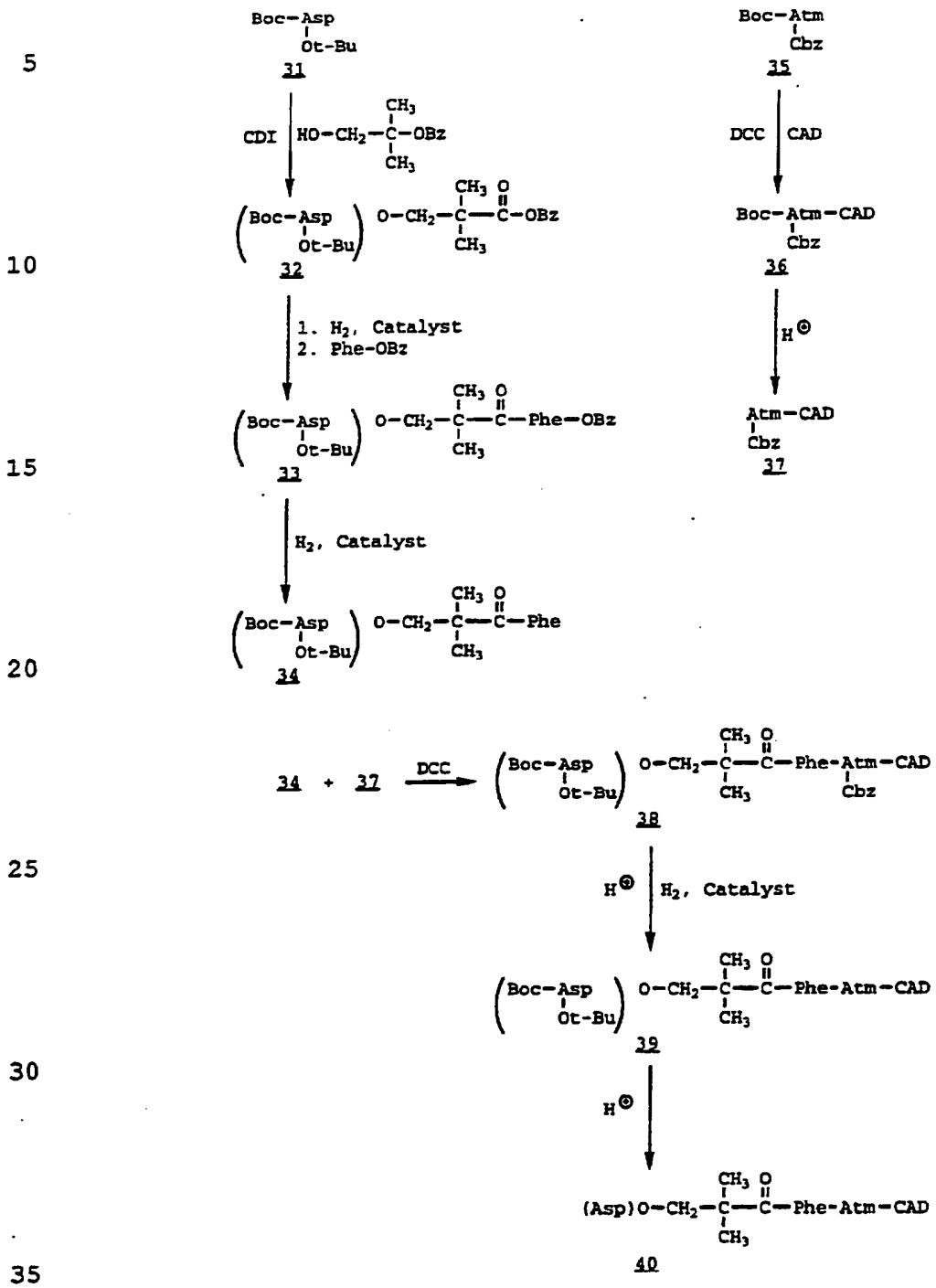

19a or 19b
1. $(H_3CO)_2C-(CH_3)_2$
$H^{\oplus}$
2. $H_2$/catalyst
SMO
N
$CH_2$
$H_3C$
$H_3C$
O
$(CH_2)_3-CH_3$

25

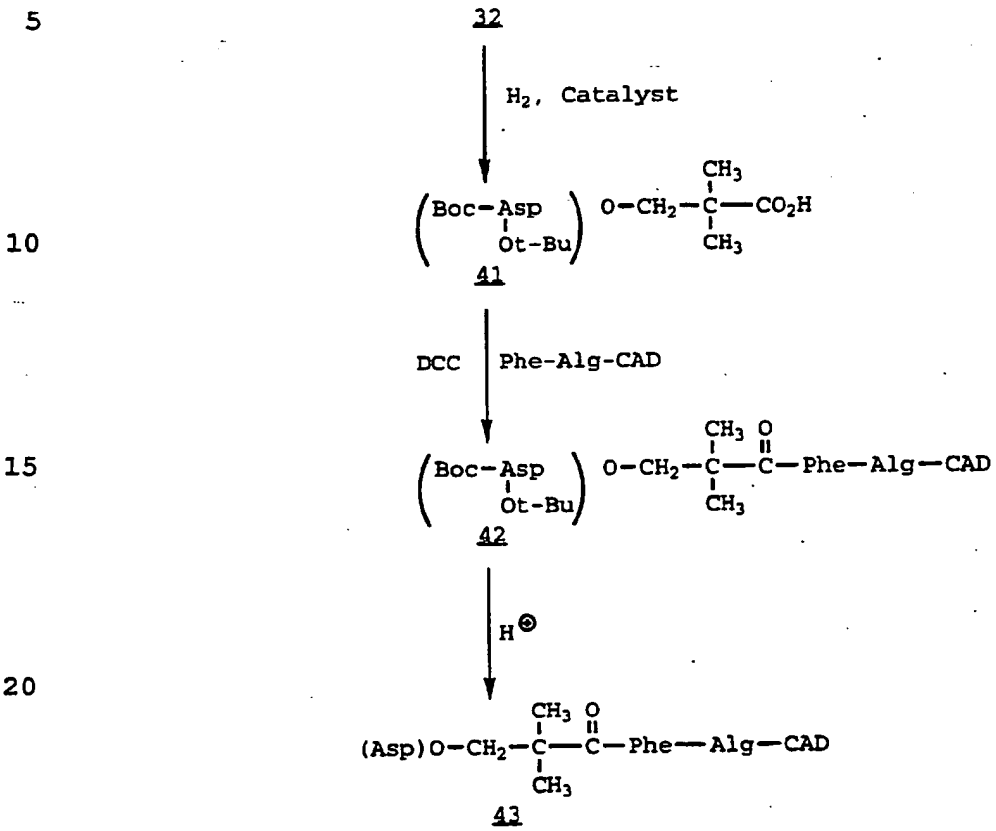
SCHEME 4


19a (R-isomer)
19b (S-isomer)
Cbz-Asp
OBz
26
CH2Ph
SMO-NH-CH-CH-CH2CH2CH=CH2
O(Asp-Cbz)
OBz
(R-isomer)
27a
(S-isomer)
27b
NaIO4
RuO2
SMO-NH-CH-CH-CH2CH2CO2H
(R-isomer)
28a
(S-isomer)
28b
CAD
SMO-NH-CH-CH-CH2-CH2-C-CAD
(R-isomer)
29a
(S-isomer)
29b
H2
Catalyst
SMO-NH-CH-CH-CH2-CH2-C-CAD
O(Asp)
(R-isomer)
30a
(S-isomer)
30b

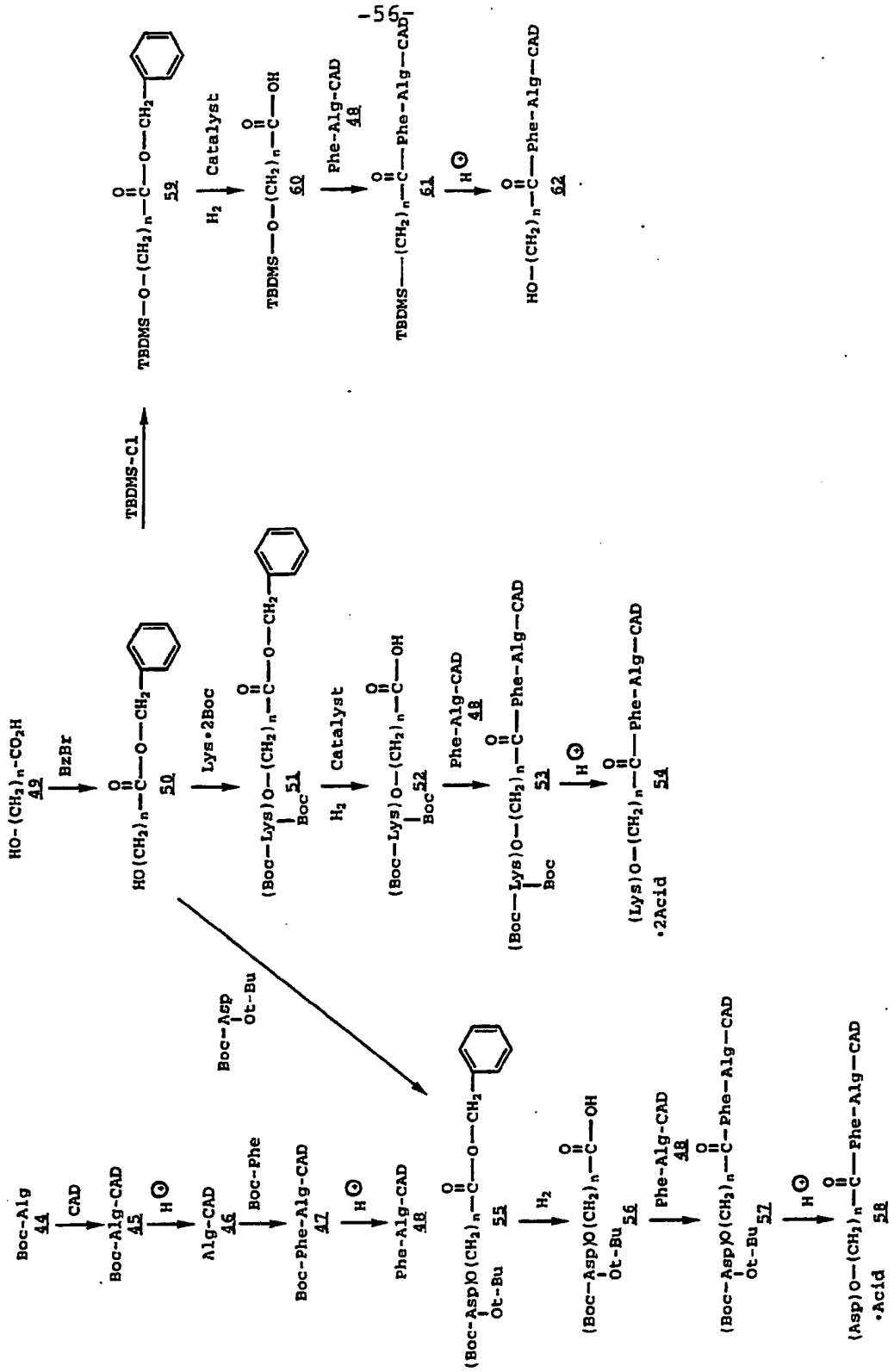
SCHEME 5


Boc-Asp
Ot-Bu
31
CDI
HO-CH2-C(CH3)2-OBz
Boc-Asp
Ot-Bu
O-CH2-C(CH3)2-C(=O)-OBz
32
1. H2, Catalyst
2. Phe-OBz
Boc-Asp
Ot-Bu
O-CH2-C(CH3)2-C(=O)-Phe-OBz
33
H2, Catalyst
Boc-Asp
Ot-Bu
O-CH2-C(CH3)2-C(=O)-Phe
34
Boc-Atm
Cbz
35
DCC
CAD
Boc-Atm-CAD
Cbz
36
H⊙
Atm-CAD
Cbz
37
34 + 37
DCC
Boc-Asp
Ot-Bu
O-CH2-C(CH3)2-C(=O)-Phe-Atm-CAD
Cbz
38
H⊙
H2, Catalyst
Boc-Asp
Ot-Bu
O-CH2-C(CH3)2-C(=O)-Phe-Atm-CAD
39
H⊙
(Asp)O-CH2-C(CH3)2-C(=O)-Phe-Atm-CAD
40

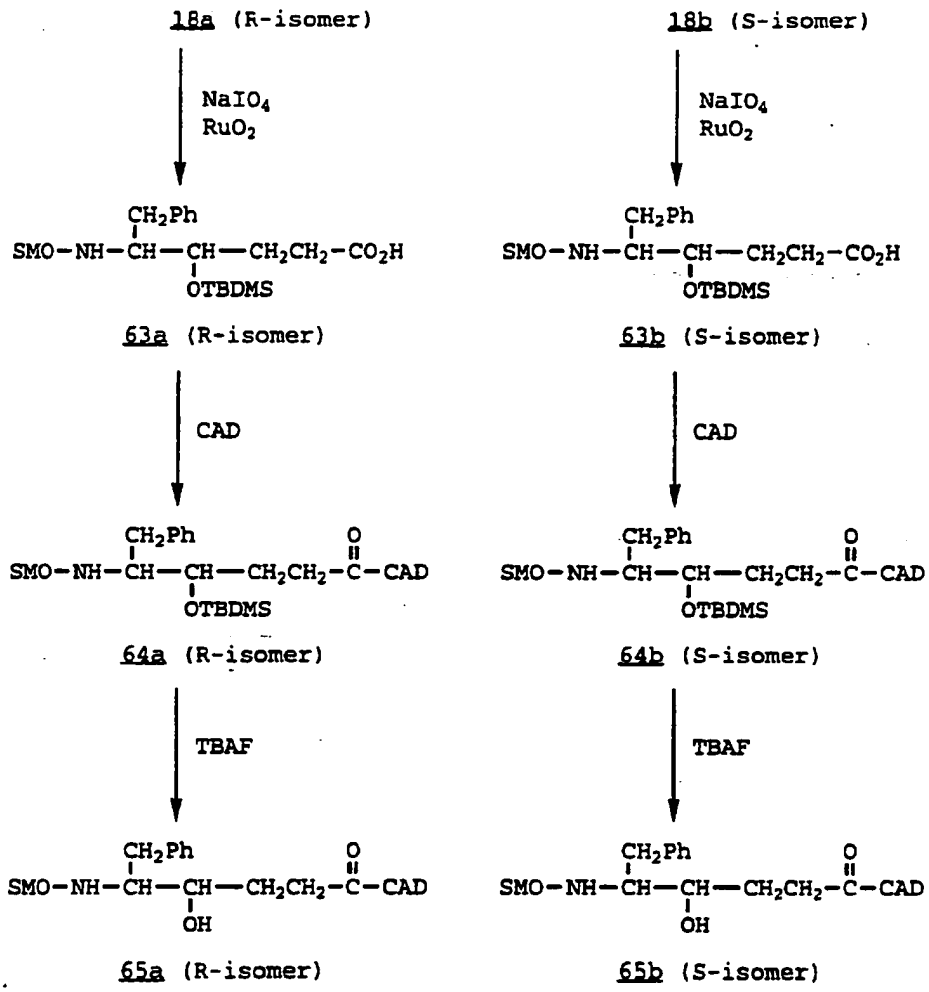
SCHEME 6


32
H2, Catalyst
Boc-Asp
Ot-Bu
O-CH2-C(CH3)2-CO2H
41
DCC
Phe-Alg-CAD
42
H⊕
(Asp)O-CH2-C(CH3)2-C(=O)-Phe-Alg-CAD
43

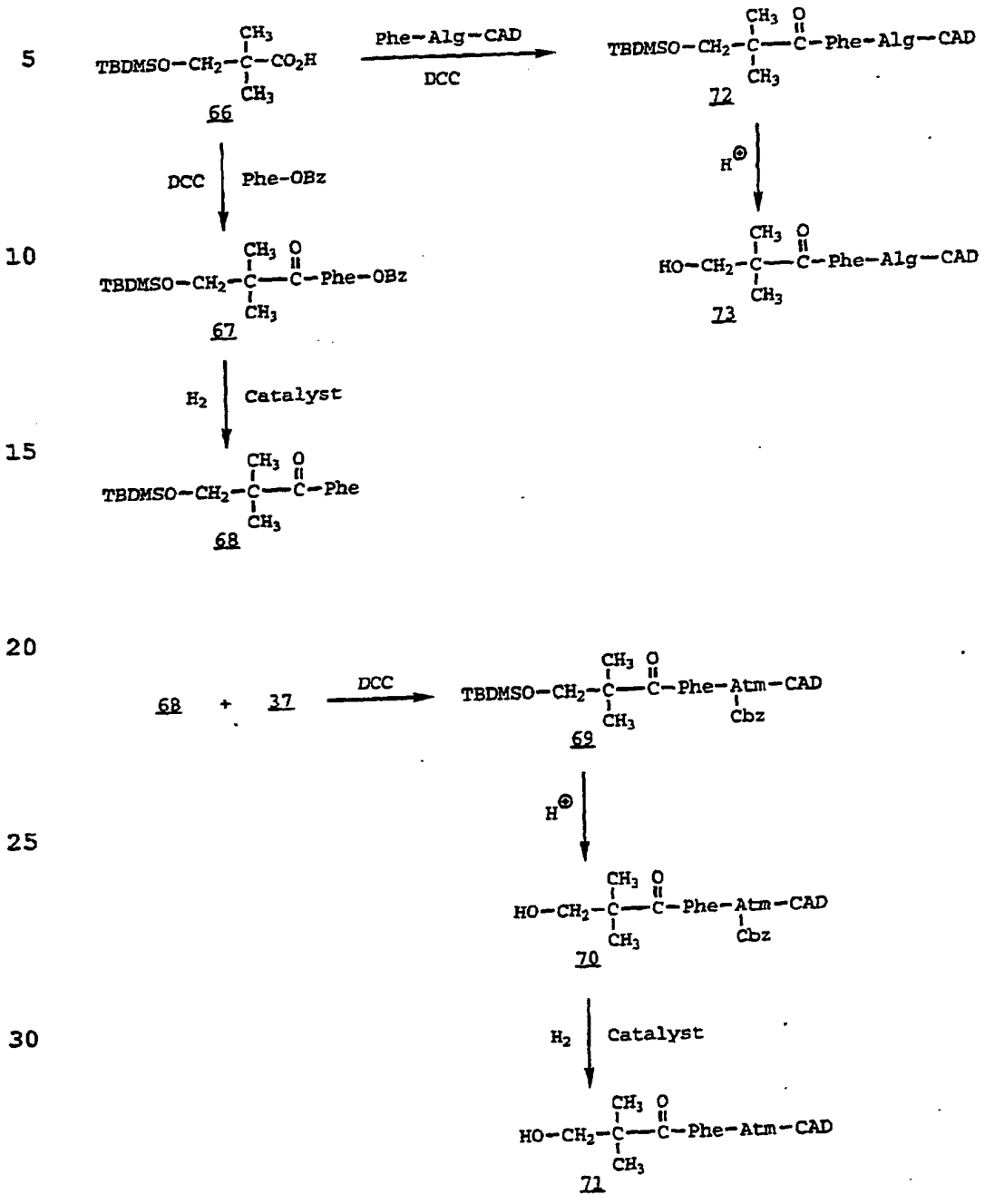
SCHEME 7


HO-(CH2)n-CO2H
42
BzBr
HO(CH2)n—C(=O)—O—CH2
50
Lys•2Boc
(Boc—Lys)O—(CH2)n—C(=O)—O—CH2
Boc 51
H2
Catalyst
(Boc—Lys)O—(CH2)n—C(=O)—OH
Boc 52
Phe-Alg-CAD
48
(Boc—Lys)O—(CH2)n—C(=O)—Phe-Alg—CAD
Boc 53
H⊙
(Lys)O—(CH2)n—C(=O)—Phe-Alg—CAD
•2Acid 54
TBDMS-Cl
TBDMS—O—(CH2)n—C(=O)—O—CH2
59
H2
Catalyst
TBDMS—O—(CH2)n—C(=O)—OH
60
Phe-Alg-CAD
48
TBDMS—(CH2)n—C(=O)—Phe-Alg—CAD
61
H⊙
HO—(CH2)n—C(=O)—Phe-Alg—CAD
62
Boc-Alg
44
CAD
Boc-Alg-CAD
45
H⊙
Alg-CAD
46
Boc-Phe
Boc-Phe-Alg-CAD
47
H⊙
Phe-Alg-CAD
48
Boc-Asp
Ot-Bu
(Boc-Asp)O(CH2)n—C(=O)—O—CH2
Ot-Bu 55
H2
(Boc-Asp)O(CH2)n—C(=O)—OH
Ot-Bu 56
Phe-Alg-CAD
48
(Boc-Asp)O(CH2)n—C(=O)—Phe-Alg—CAD
Ot-Bu 57
H⊙
(Asp)O—(CH2)n—C(=O)—Phe-Alg—CAD
•Acid 58

SCHEME 8


18a (R-isomer)
18b (S-isomer)
NaIO4
RuO2
CH2Ph
SMO-NH-CH-CH-CH2CH2-CO2H
OTBDMS
63a (R-isomer)
63b (S-isomer)
CAD
O
SMO-NH-CH-CH-CH2CH2-C-CAD
64a (R-isomer)
64b (S-isomer)
TBAF
OH
65a (R-isomer)
65b (S-isomer)

SCHEME 9


TBDMSO-CH2-C(CH3)2-CO2H
66
Phe-Alg-CAD
DCC
TBDMSO-CH2-C(CH3)2-C(=O)-Phe-Alg-CAD
72
DCC
Phe-OBz
H⊕
TBDMSO-CH2-C(CH3)2-C(=O)-Phe-OBz
67
HO-CH2-C(CH3)2-C(=O)-Phe-Alg-CAD
73
H2
Catalyst
TBDMSO-CH2-C(CH3)2-C(=O)-Phe
68
68 + 37
DCC
TBDMSO-CH2-C(CH3)2-C(=O)-Phe-Atm-CAD
Cbz
69
H⊕
HO-CH2-C(CH3)2-C(=O)-Phe-Atm-CAD
Cbz
70
H2
Catalyst
HO-CH2-C(CH3)2-C(=O)-Phe-Atm-CAD
71

Preferred methods for the preparation of compounds of Formula I are described in Schemes 1 to 7.

Compounds of Formula I are designated by numbers 8, 11, 14, 24a, 24b, 30a, 30b, 40, 43, 54, an 58.

These schemes illustrate preferred methods from which a person, skilled in the art of organic chemistry, could analogously prepare all compounds of Formula I.

Compounds of Formula I designated 8, 11, and 14 are prepared from a compound of Formula 1 as outlined in Scheme I. Thus, SMO-Cl(1)(morpholinosulfamyl chloride) (prepared according to the method of R. Wegler and K. Bodenbenner, Annalen der Chemie, 624, 25 (1959)) is reacted with Phe in the presence of a base such as, for example, $Et_3N$ and the like and a solvent such as, for example, $CH_2Cl_2$ and the like at about -30°C to about 100°C for about one to 24 hours to give the compound of Formula 2. Preferably, the reaction is carried out in the presence of $Et_3N$ and $CH_2Cl_2$ at about 25°C for about 2 to 6 hours. Treatment of Cbz-Ser (3) with CAD in the presence of a coupling reagent such as, for example, DCC and HOBT and the like and a solvent such as, for example, $CH_2Cl_2$, $CHCl_3$, THF and the like optionally in the presence of an aprotic solvent such as, for example, DMF, DMSO and the like at about 0°C to about 25°C for about 6 hours to about 5 days to give the compound of Formula 4. The compound of Formula 4 is treated with hydrogen in the presence of a catalyst such as, for example, 5% to 20% palladium on carbon, platinum oxide, 5% to 20% platinum on carbon, and the like in a solvent such as, for example, EtOH, EtOAc, THF, dioxane, DMF and the like at about 0°C to about 100°C for about 30 minutes to about 24 hours to give the compound of Formula 5. The compound of Formula 2 is reacted with the compound of Formula 5 in the

presence of a coupling reagent such as, for example, DCC and HOBT and the like and a solvent such as, for example, $CHCl_3$, $CH_2Cl_2$, THF, dioxane, EtOAc, DMF, DMSO and the like at about 0°C to about 40°C for about 1 to 5 days to give the compound of Formula 6. The compound of Formula 6 is reacted with LYS.2BOC in the presence of a coupling reagent such as, for example, CDI, DCC, and the like in the presence of a solvent such as, for example, $CHCl_3$, $CH_2Cl_2$, THF, dioxane, EtOAc, DMF, DMSO and the like at about 0°C to about 100°C for about 3 hours to about 3 days to give the compound of Formula 7. The compound of Formula 7 is treated with an acid such as, for example, trifluoroacetic acid, or a nonpolar inert solvent such as $CH_2Cl_2$ saturated with hydrogen chloride gas at about -20°C to about 25°C for about 1 to 5 hours to give the compound of Formula 8.

In a similar manner the compound of Formula 6 is reacted with Cbz-Gln or Cbz-Glu(OBz) to afford,

respectively, a compound of Formula 10 and a compound of Formula 13. Compounds of Formula 10 and 13 are reacted with hydrogen in the presence of a catalyst such as for example 50% palladium on carbon and an acid such as for example TFA and the like in a solvent such as for example ethanol and the like to afford, respectively, a compound of Formula 11 and a compound of Formula 14.

Compounds of Formula I designated 24a and 24b are prepared from a compound of Formula 2 as outlined in Scheme 2. Thus, the compound of Formula 2 is reacted with a coupling reagent such as, for example, CDI and the like in a solvent such as THF, $CH_2Cl_2$, mixtures thereof and the like followed by O,N-dimethylhydroxylamine hydrochloride and a base such as, for example, N-methylpiperidine and the like to give the compound of Formula 15. The compound of

Formula 15 is added to the magnesium Grignard reagent of 4-bromo-1-butene in a solvent such as, for example, THF, $Et_2O$ and the like to give the compound of Formula 16. The compound of Formula 16 is treated with a hydride reagent such as, for example, $KBH_4$ and the like in a solvent such as, for example, absolute EtOH and the like to give the compound of Formula 17 as a mixture of R and S isomers at the carbon atom to which the hydroxyl group is attached. Choice of solvent and reducing reagent can vary the ratio of isomers obtained to give a predominant excess of a particular desired isomer. The R and S isomers of the compound of Formula 17 may be separated into the individual R and S isomers by conventional separation techniques such as, for example, chromatography, fractional crystallization and the like. Alternatively, the compound of Formula 17 (R and S mixture of isomers) is reacted with t-butyldimethylsilyl chloride (TBDMS-Cl) in the presence of imidazole and DMF to give the compound of Formula 18 as a mixture of R and S isomers at the carbon atom to which the O-TBDMS group is attached. The R and S isomers of the compound of Formula 18 may be separated into the individual R and S isomers by conventional separation techniques such as, for example, chromatography and the like. Additionally, other hydroxyl protecting groups such as, for example, acetyl, benzyl, and the like may be used in place of the TBDMS group with subsequent separation of the R and S protected hydroxyl groups following the methodology used to separate the isomers of the compound of Formula 18. Either the compound of Formula 18a (R-isomer) or Formula 18b (S-isomer) is reacted with a fluoride ion source such as, for example, t-butylammonium fluoride and the like in a solvent such as, for example, THF and the like to give the compound of Formula 19a (R-isomer) or

Formula 19b (S-isomer). Either the compound of Formula 19a (R-isomer) or Formula 19b (S-isomer) is reacted with the imidazolide of N-α-Boc-ε-CBZ-LYS (prepared from Nα-Boc-ε-Cbz-Lys, CDI and DMAP) (optionally compatible N-protecting groups other than Boc or Cbz may also be used to protect the amino groups of Lys) in a solvent such as, for example, $CH_2Cl_2$ and the like at about ambient temperature to give the compound of Formula 20a (R-isomer) or Formula 20b (S-isomer). Either the compound of Formula 20a (R-isomer) or Formula 20b (S-isomer) is treated with an oxidizing reagent such as, for example, $NaIO_4$ with a catalytic amount of $RuO_2$, and the like to give the compound of Formula 21a (R-isomer) or Formula 21b (S-isomer). Either the compound of Formula 21a (R-isomer) or Formula 21b (S-isomer) is reacted with CAD in the presence of a coupling reagent such as, for example, DCC and HOBT and the like in a solvent such as, for example, $CH_2Cl_2$, $CHCl_3$, THF and the like, optionally an aprotic solvent such as, for example, DMF, DMSO and the like is added to aid solution, at about 0°C to about 25°C for about 4 hours to about 3 days to give the compound of Formula 22a (R-isomer) or Formula 22b (S-isomer). Either the compound of Formula 22a (R-isomer) or Formula 22b (S-isomer) is treated with hydrogen in the presence of a catalyst such as, for example, 5% to 20% palladium on carbon, platinum oxide, 5% to 20% platinum on carbon, platinum oxide, 5% to 20% platinum on carbon, and the like in a solvent such as, for example, EtOH and the like to give the compound of Formula 23a (R-isomer) or Formula 23b (S-isomer). Either the compound of Formula 23a (R-isomer) or Formula 23b (S-isomer) is treated with an acid such as, for example, trifluoroacetic acid, a nonpolar inert solvent such as, for example, $CH_2Cl_2$ and the like saturated with

hydrogen chloride gas to give the compound of Formula 24a (R-isomer) or Formula 24b (S-isomer) as the diacid addition salt. The diacid addition salt of the compound of Formula 24a (R-isomer) or Formula 24b (S-isomer) may be converted to other pharmaceutically acceptable acid addition salts by conventional methodology as previously described. The configuration of each isomer at the carbon atom to which the hydroxyl or derivatized hydroxyl group is attached is assigned as outlined in Scheme 3. Thus, either the compound of Formula 19a or Formula 19b is reacted with 2,2-dimethoxypropane in the presence of an acid catalyst such as, for example, para-toluenesulfonic acid and the like followed by reduction with hydrogen in the presence of a catalyst such as, for example, rhodium on carbon and the like to afford the compound of Formula 25a or Formula 25b. $^1$H-NMR decoupling determinations indicate the stereochemistry of the protons attached to the five-membered ring.

Compounds of Formula I designated 30a and 30b are prepared, respectively, from a compound of Formula 19a and 19b as outlined in Scheme 4 using the methodology used to prepare compounds of Formula 24a and 24b from compounds of Formula 19a and 19b as described in Scheme 2.

A compound of Formula I designated as 40 is prepared from a compound of Formula 31 as outlined in Scheme 5.

A compound of Formula I designated as 43 is prepared from a compound of Formula 32 as outlined in Scheme 6.

Compounds of Formula I designated 54 and 58 are prepared respectively from a compound of Formula 49 and a compound of Formula 44 as outlined in Scheme 7.

The preparation of selected parent renin inhibitors of compounds of Formula I designated as

65a, 65b, 71, and 73 are as outlined in Schemes 8 and 9.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active

component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 2000 mg preferably 0.5 mg to 1000 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents for treating hypertension, hyperaldosteronism, congestive heart failure, and diseases caused by retroviruses including HTLV I, II, and III as well as diagnostic tools for the identification of cases of hypertension due to renin excess, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.1 mg to about 50 mg per kilogram daily. A daily dose range of about 0.5 mg to about 30 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the

total daily dosage may be divided and administered in portions during the day, if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

**EXAMPLE 1**

**SMO-Phe-Ser(Lys·2HCl)-CAD**

**Step A: Preparation of SMO-Phe-Ser(Lys·2 Boc)-CAD**

Di-t-Boc-Lys (1.11 g, 3.19 mmol, 2.0 eq) in THF (7 mL) is added to CDI (570 mg, 3.51 mmol, 2.2 eq) in THF (7 mL) at 0°C under $N_2$ and stirred for 30 minutes. SMO-Phe-Ser-CAD (Example C) (1.0 g, 1.60 mmol) in THF (5 mL) is added and the mixture stirred at room temperature for 3 days. The solvents are evaporated and the residue partitioned between ethyl acetate (50 mL) and 2N HCl (50 mL). The organic layer is separated, washed with 2N sodium carbonate (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and evaporated to afford a white foam. This is purified by column chromatography on silica gel eluting with 2% then 3% MeOH/$CH_2Cl_2$ to give a white foam. This is further purified by column chromatography on silica gel (thin layer chromatography - TLC grade) eluting with 3% methanol/dichloromethane to give 699 mg of a white foam.

$^1H$ NMR (300 MHz, $d^6$DMSO + 2 drops $D_2O$) δ 8.56 (1H, d, J = 9Hz), 7.69 (1H, d, J = 10 Hz), 7.10-7.40 (6 H, m), 6.72 (1H, br t), 4.61 (1H, m), 4.10-4.30 (3H, m), 3.95 (2H, m), 3.35 (4H, m), 3.41 (1H, t, J = 9 Hz), 2.80-3.00 (4H, m), 2.55-2.75 (5 H, m), 1.00-1.80 (40H, m), 0.86 (3H, d, J = 7.2 Hz), 0.78 (3H, d, J = 7.0 Hz).

**Step B: Preparation of SMO-Phe-Ser(Lys·2 HCl)-CAD**

SMO-Phe-Ser(Lys·2Boc)-CAD (600 mg, 0.628 mmol) in $CH_2Cl_2$ (5 mL) is added to $CH_2Cl_2$ (20 mL) saturated with HCl (gas) at 0°C and stirred at 0°C for 2 hours. The solvents are evaporated and the residue taken up in water (30 mL) and washed with chloroform (3 x 20 mL). The water layer is filtered through 'hyflo' and freeze-dried to give 425 mg of a white powder. Mass spectrum-fast atom bombardment (MS (FAB)) 755.2 (100%) - free base $M^+$

**EXAMPLE 2**

**SMO-Phe-Ser(Asp·HCl)-CAD**

**Step A: Preparation of SMO-Phe-Ser(Asp·Boc·t-Bu)-CAD**

γ-t-Bu(N-Boc) aspartate dicyclohexylammonium salt (1.50 g, 3.19 mmol, 4 eq) is added to 5% citric acid (100 mL) and extracted with ethyl acetate (3 x 50 mL), the extracts are washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated to an oil. This is dissolved in THF (5 mL) and added to CDI (569 mg, 3.51 mmol, 4.4 eq) at 0°C and stirred for 1 hour. Smo-Phe-Ser-CAD (Example C) (0.5 g, 0.80 mmol) in THF (2 mL) is added and the mixture stirred for 1 week. The mixture is diluted with EtOAc (30 mL), washed with 5% citric acid solution (50 mL), 2 N $Na_2CO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and evaporated to leave a brown solid. This is purified by column chromatography (2% to 3% MeOH/$CH_2Cl_2$) to afford the product as white foam (573 mg). Further chromatography (2% MeOH/$CH_2Cl_2$, TLC silica) affords 277 mg of a white solid. $^1H$ NMR (300 MHz, $d^6$-DMSO + 2 drops $D_2O$) δ 7.20-7.40 (6H, m), 4.62 (1H, t, J = 5.8 Hz), 4.40 (1H, dd, J = 9.7, 3.5 Hz), 4.10-4.30 (3H, m), 3,94 (1H, dd, J = 11.2, 3,3 Hz), 3.34 (4H, br s), 3.06 (1H, t, J = 5.2 Hz), 2.85-3.00 (2H, m), 2.40-

2.75 (8H, m), 1.00-1.80 (34H, m), 0.84 (3H, d, J = 6.7 Hz), 0.78 (3H, d, J = 6.4 Hz).

**Step B: Preparation of SMO-Phe-Ser(Asp·HCl)-CAD**

Hydrogen chloride gas is passed over the aspartate (588 mg, 0.65 mmol) in $CH_2Cl_2$ (20 mL) at room temperature and stirred for 1 hour. The solvent is evaporated and the residue dissolved in $CHCl_3$. This is evaporated to leave a white solid. This is dissolved in water (150 mL) and washed with EtOAc (100 mL). Hexane (50 mL) is added to break down the emulsion that forms and the aqueous layer filtered through celite and evaporated to afford 447 mg of a white solid. $^1H$ NMR (200 MHz, $d^6$-DMSO + 2 drops $D_2O$) 7.20-7.40 (6H, m), 4.91 (1H, t, J = 5.0 Hz), 4.82 (1H, d, J = 6.0 Hz), 4.46 (2H, m), 4.12 (1H, brt, J = 5.0 Hz), 3.69 (1H, brm), 3.34 (4H, br s), 2.50-3.10 (11H, m), 1.00-1.80 (15H, m), 0.95 (3H, d, J = 7.0 Hz).

## EXAMPLE 3

## SMO-Phe-Thr(Lys·2HCl)-CAD

**Step A: Preparation of SMO-Phe-Thr(Lys·2Boc)-CAD**

Di-t-Boc-Lys (5.41 g, 15.6 mmol, 5 eq) in THF (20 mL) is added to CDI (3.04 g, 18.7 mmol, 6 eq) in THF (20 mL) at 0°C under $N_2$. After stirring at 0°C for 5 min, the solution becomes homogenous. TLC confirmed no lysine present. SMO-Phe-Thr-CAD (Example D) (1.926 g, 3.00 mmol) in THF (20 mL) and DMAP (100 mg) are added at 0°C. The mixture is stirred at room temperature overnight and then at reflux for 24 hours. The cooled mixture is evaporated, the residue taken up in EtOAc (300 mL), washed with 2 N HCl (200 mL), 2 N $Na_2CO_3$ (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and evaporated to leave a white foam (~8 g). This is

purified by column chromatography on silica gel (flash) eluting with 2% then 3% MeOH/$CH_2Cl_2$ to give a white foam (2.93 g). This is further purified by column chromatography twice on silica gel (2 x 100 g TLC grade) to afford 578 mg of a white foam. HPLC 98.6% pure.

**Step B: Preparation of SMO-Phe-Thr(Lys·2HCl)-CAD**

The lysine ester (600 mg) in $CH_2Cl_2$ (5 mL) is added to saturated HCl/$CH_2Cl_2$ (20 mL) at 0°C and the mixture stirred at room temperature for 4 hours. The solvent is evaporated to leave the product as an off-white solid. This is dissolved in water (50 mL) and washed with EtOAc (50 mL), filtered through celite and freeze-dried to afford 454 mg of a fluffy white solid. MS (FAB) 769.5 (17%) $M^+$ of free base.

**EXAMPLE 4**

**SMO-Phe-Ser(Glu·TFA)-CAD**

**Step A: Preparation of SMO-Phe-Ser(Glu·Cbz)-CAD**


A mixture of SMO-Phe-Ser-CAD (Example C) (300 mg, 0.479 mmol), Glu·Cbz·Bz (178 mg, 0.479 mmol), DDC (99 mg, 0.479 mmol), and DMAP (12 mg, 95.7 µmol) in dichloromethane (5 mL) is stirred at room temperature for 16 hours. The mixture is filtered and evaporated to leave an oil. The oil is purified by column chromatography on silica gel (50 g TLC grade) eluting with 2% methanol/dichloromethane to give 347 mg of a white solid; MS (FAB) 980.6 (42%) M+.

**Step B: Preparation of SMO-Phe-Ser(Glu·TFA)-CAD**

SMO-Phe-Ser(Glu·Cbz)-CAD (340 mg, 0.347 mmol) is


stirred in ethanol (20 mL) with 5% palladium on carbon (120 mg) and TFA (134 µL, 1.73 mmol) under

hydrogen. After 6 hours the mixture is filtered through hyflo and evaporated to leave an oil. This oil is dissolved in water (50 mL) and ethanol (30 mL), filtered through hyflo, and evaporated to remove the ethanol. The remaining aqueous phase is freeze-dried to give a white solid. This solid is dried to 50°C under high vacuum to give 277 mg of a white solid; MS (FAB) 756.5 (100%) M+.

**EXAMPLE 5**

**SMO-Phe-Ser(Gln·TFA)-CAD**

**Step A: Preparation of SMO-Phe-Ser(Gln·Cbz)-CAD**

SMO-Phe-Ser-CAD (Example C) (300 mg, 0.479 mmol) is reacted with Gln·Cbz (134 mg, 0.479 mmol) under the same conditions in Example 4, Step A to give 392 mg of a colorless oil;
$^1$H NMR (300 MHz, d$^6$-DMSO + two drops $D_2O$):
δ 7.15-7.50 (11H, m), 5.01 (2H, s), 4.65 (1H, t, J = 6.1 Hz), 3.90-4.35 (5H, m), 3.35 (4H, s), 3.11 (1H, t, J = 9.2 Hz), 2.95 (2H, m), 2.15 (2H, t, J = 7.3 Hz), 0.95-2.05 (18H, m), 0.83 (3H, d, J = 6.6 Hz), 0.78 (3H, d, J = 6.2 Hz).

**Step B: Preparation of SMO-Phe-Ser(Gln·TFA)-CAD**

SMO-Phe-Ser(Gln·Cbz)-CAD (305 mg, 0.343 mmol) is reacted under the same conditions in Example 4, Step B to give 252 mg of a white powder;
$^1$H NMR (300 MHz, d$^6$-DMSO + two drops $D_2O$): δ 8.67 (1H, d, J = 7.9 Hz), 7.72 (1H, d, J = 9.2 Hz), 7.15-7.40 (6H, m), 4.72 (1H, q, J = 6.7 Hz), 3.85-4.40 (5H, m), 3.34 (4H, s), 2.95-3.15 (3H, m), 2.45-2.75 (6H, m), 2.27 (2H, m), 2.02 (2H, m), 0.95-1.85 (15H, m), 0.86 (3H, d, J = 6.6 Hz), 0.79 (3H, d, J = 6.6 Hz).

**EXAMPLE 6**

**SMO-Phe-Ser(Ala·TFA)-CAD**

**Step A: Preparation of SMO-Phe-Ser(Ala-Cbz)-CAD**

A mixture of SMO-Phe-Ser-CAD (Example C) (300 mg, 0.468 mmol), Cbz-Ala (105 mg, 0.468 mmol, 1.0 eq), DCC (97 mg, 0.468 mmol, 1.0 eq) and DMAP (11 mg, 94 µmol, 0.2 eq) in dichloromethane (10 mL) is stirred at room temperature for 16 hours. The mixture is filtered and evaporated. The residue is purified by column chromatography on silica gel (50 g TLC grade) eluting with 2% methanol in dichloromethane to give 407 mg of a colorless oil; MS (FAB) 832.2 (36%) $M^+$.

**Step B: Preparation of SMO-Phe-Ser(Ala·TFA)-CAD**

A mixture of SMO-Phe-Ser(Ala-Cbz)-CAD (349 mg, 0.419 mmol), 5% palladium on carbon (100 mg) and trifluoroacetic acid (162 µL, 5 eq) in ethanol (50 mL) is stirred under hydrogen for 4 hours. The mixture is filtered through 'Hyflo' (diatomaceous earth) and evaporated to a white residue. This is dissolved in 1:1 ethanol:water (100 mL), filtered through 'Hyflo' and evaporated until all of the ethanol has gone. The residue is freeze-dried to afford a white powder (292 mg); MS (FAB) 698.2 (100%) $M^+$ of free base.

**EXAMPLE 7**

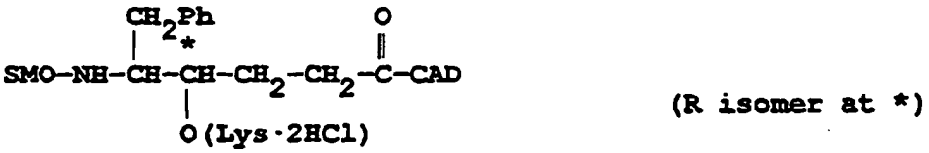
**SMO-Phe-Mal-CAD(2·$COCH_2CH_2CO_2H$)**

A mixture of SMO-Phe-Mal-CAD (U.S. 5,036,053) (200 mg, 0.305 mmol), succinic anhydride (153 mg, 1.53 mmol, 5 eq) and DMAP (75 mg, 0.611 mmol, 2 eq) is stirred in $CH_2Cl_2$ (2.5 mL) at room temperature for 2 days. The solvent is evaporated and the residue taken up in EtOAC (30 mL) and washed with 2 N HCl (2 x 20 mL). The EtOAc layer is washed with brine (30 mL), dried ($MgSO_4$), filtered and evaporated to

leave a yellow foam. This is purified by column chromatography on silica gel eluting with 5% MeOH/0.5% HOAc/$CH_2Cl_2$ to afford 2.04 mg of a white foam.

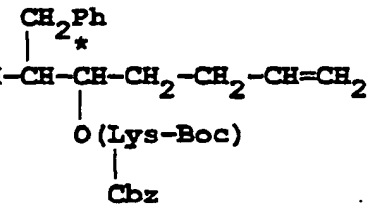
TLC silica gel plates (5% methanol/ dichloromethane/1% HOAc) Rf 0.39; detection UV and phosphomolybdic acid. $^1H$ NMR (300 MHz, $d^6$-DMSO) δ 12·15 (2H, brs), 8.87 (1H, 2 x d, J = 10.0 Hz), 8.31 (1H, d, J = 10.0 Hz), 7.73 (1H, t, J = 11.0 Hz), 7.15-7.50 (5H, m), 5.20 (1H, t, J = 9.0 Hz), 4.95 (2H, m), 4.20 (2H, m), 3.73 (3H, 2 x s), 3.03 (1H, m), 2.91 (1H, m), 2.35-2.75 (13H, m), 0.6-1.80 (21H, m).

## EXAMPLE 8



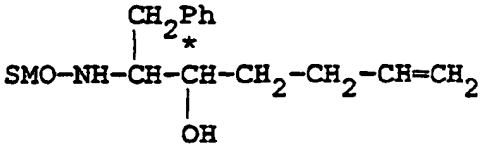

(R isomer at *)

**Step A: Preparation of**




(R isomer at *)

Alpha-Boc,epsilon-Cbz-Lys, 2.15 g (5.64 mmol), is dissolved in 75 mL dry dichloromethane and cooled to 5°C. CDI (1.05 g, 6.49 mmol), is added, and the mixture is warmed to 25°C over 1 hour.




(Example I)

(R isomer at *), (2.0 g, 5.64 mmol) is dissolved in dichloromethane (50 mL), and is added to the previously prepared solution. A trace of DMAP is added, and the mixture is stirred at 25°C for 2 weeks. The mixture is then consecutively washed

with 1N citric acid, saturated NaCl solution, saturated $NaHCO_3$ solution and saturated NaCl solution. The organic phase is dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a glassy solid, 4.02 g. Chromatography of the solid on silica gel eluting with EtOAc/hexane (25/75) gives the R isomer product as a white foam, 2.88 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 617.4 (100%) $M^+$-Boc.

In a similar manner, SMO-NH-CH($CH_2Ph$)*-CH(OH)-$CH_2$-$CH_2$-CH=$CH_2$ (S isomer at *) (2.0 g, 5.64 mmol) gives the desired S isomer product as a white foam, 2.65 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 617.4 (100%) $M^+$-Boc.

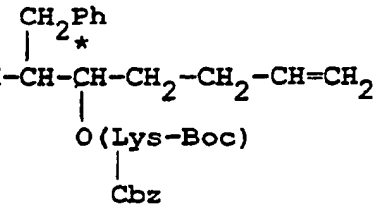
**Step B: Preparation of SMO-NH-CH($CH_2Ph$)*-CH(O(Lys-Boc)-Cbz)-$CH_2$-$CH_2$-$CO_2H$**

**(R isomer at *)**

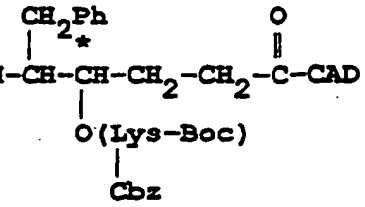
SMO-NH-CH($CH_2Ph$)*-CH(O(Lys-Boc)-Cbz)-$CH_2$-$CH_2$-CH=$CH_2$ (R isomer at *)

(2.66 g, 3.71 mmol) is dissolved in 100 mL acetone and cooled to 3°C. In a separate flask, $NaIO_4$ (5.52 g, 25.8 mmol) and ruthenium (IV) oxide hydrate (0.168 g) are dissolved in 65 mL $H_2O$. The solution is filtered and added to the previous solution, giving an exotherm to 28°C. Temperature is maintained by cooling at 25°C for 1.5 hours, after which isopropanol (5 mL) is added. After stirring for 15 minutes, the mixture is filtered, evaporated

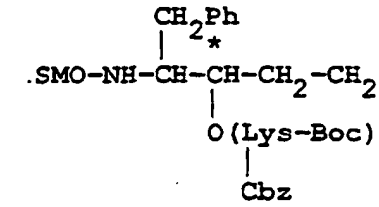
to an oily aqueous suspension, diluted with saturated NaCl solution and extracted into $CHCl_3$. The organic extract is washed with a dilute $Na_2SO_3$ solution and the pH adjusted to 2.0 with 1 N HCl. The organic phase is washed with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated to give the R isomer product as a white foam, 2.08 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 735.3 (4.65%) $M^+$.

Similar treatment of 

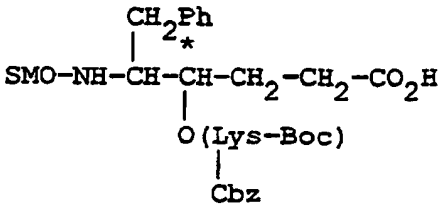
(S isomer at *), 2.48 g (3.46 mmol) gives the corresponding S isomer product as a white foam, 2.11 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 735.5 (3.8%) $M^+$.

**Step C: Preparation of** 

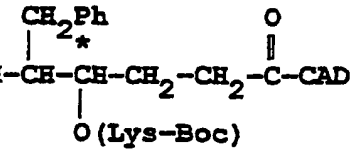
**(R isomer at *)**

 (R isomer at *) (1.90 g, 2.58 mmol) is dissolved in dichloromethane (100 mL). A solution of HOBT (0.36 g, 2.66 mmol) in 5 mL DMF is added followed by a solution of CAD (0.63 g, 2.58 mmol in dichloromethane (25 mL). The mixture is stirred and allowed to warm to 25°C overnight. The mixture is filtered and evaporated under reduced pressure. The residue is taken up into EtOAc and

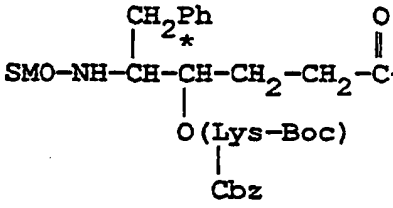
washed consecutively with solutions of saturated NaCl, 1 N citric acid, saturated $NaHCO_3$, and saturated NaCl. The organic phase is dried over $MgSO_4$, filtered, and evaporated to a foam, 2.61 g. Chromatography on silica gel eluting with EtOAc/Hexane (40/60) gives the R isomer product as a white foam, 1.57 g. The structure is confirmed by NMR and Mass Spectroscopy. MS (FAB) 960.8 (14.3%) $M^+$.

In an identical manner, 

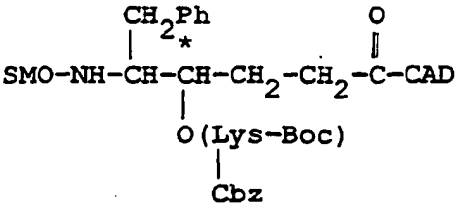
(S isomer at *) (1.90 g, 2.58 mmol), yielded 1.72 g of the corresponding S isomer product as a white foam. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 960.6 (15.1%) $M^+$.

**Step D: Preparation of** 

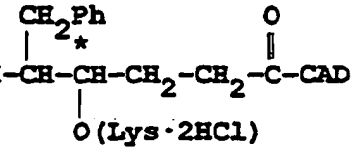
**(R isomer at *)**

 (R isomer at *) (1.45 g, 1.51 mmol) is dissolved in methanol (100 mL) and 20% palladium on carbon catalyst (0.25 g) is added. The suspension is purged with $H_2$ gas for 3 hours, filtered, and evaporated under pressure to a white foam. The foam is dissolved in a minimal amount of dichloromethane and the resulting solution is added to $Et_2O$ giving a solid precipitate. The solid is filtered, washed with $Et_2O$ and dried in vacuo to give

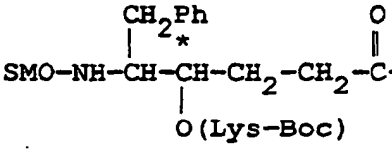
0.94 g of the R isomer product as a white solid. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 826.7 (100%) $M^+$.

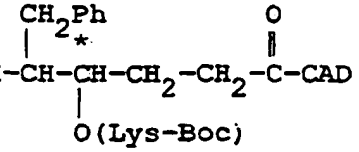
In an identical manner, 

(S isomer at *) (1.60 g, 1.67 mmol) gives the S isomer product as a white solid, 1.07 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 826.7 (100%) $M^+$.

**Step E: Preparation of** 

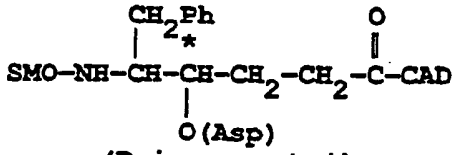
**(R isomer at *)**

 (R isomer at *) (0.92 g, 1.11 mmol) is dissolved in 25 mL dichloromethane and occasionally purged with anhydrous HCl gas. After 1 hour, the mixture is evaporated under reduced pressure to a white solid. The solid is redissolved in dichloromethane, filtered, and the filtrate is added to $Et_2O$ giving a solid precipitate. The solid is filtered, washed with $Et_2O$ and dried under reduced pressure giving the R isomer product as a white solid, 0.807 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 726.4 (100%) $M^+$.

In a similar manner, 

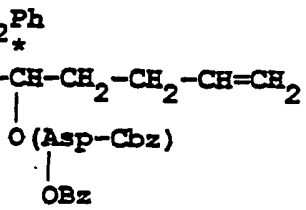
(S isomer at *) (1.05 g, 1.27 mmol) gives the S isomer product as a white solid, 0.884 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 726.3 (100%) $M^+$.

**EXAMPLE 9**



**(R isomer at *)**

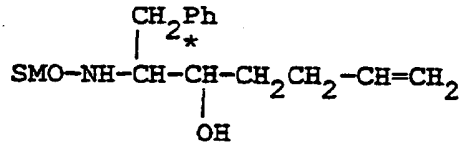
**Step A: Preparation of**



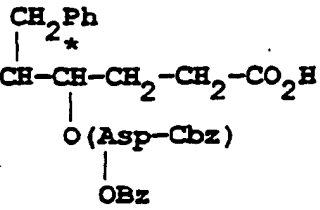
**(R isomer at *)**

Cbz-Asp 2.52 g (7.05 mmol) is dissolved in

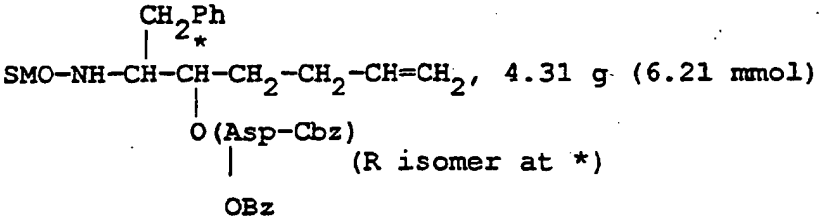
125 mL $CH_2Cl_2$, and CDI, 1.31 g (8.11 mmol) is added and stirred for 5 minutes at room temperature.



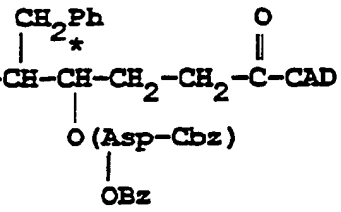
(Example I) (R Isomer at *) 2.50 g (7.05 mmol) is added, and the mixture is stirred at room temperature for 7 days. The mixture is evaporated under reduced pressure to an oil, resuspended in $Et_2O$, extracted with 1N citric acid, saturated NaCl solution, saturated $NaHCO_3$, and saturated NaCl solution. The organic phase is dried over $MgSO_4$, filtered, and evaporated to a crude gum, 4.75 g. Chromatography on silica gel, eluting with EtOAc/Hexane (20/80) gives the product as a syrup, 4.41 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 694.0 (65.2%) $M^+$.

Step B: Preparation of 

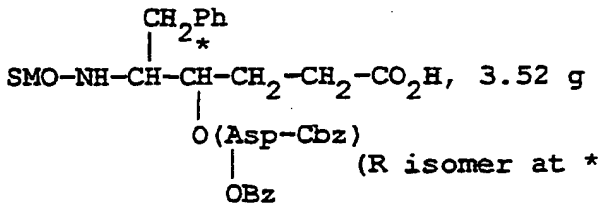
(R isomer at *)

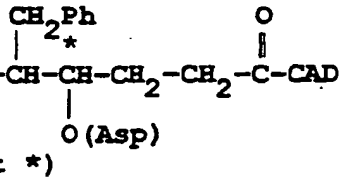


is dissolved in 170 mL acetone and cooled to 3°C. A solution of $NaIO_4$ 9.24 g (43.2 mmol) and $RuO_2xH_2O$ 0.28 g in 130 mL $H_2O$ is added to the preceding solution, giving an exotherm which is controlled to 20°C by external cooling. After stirring at room temperature for 2 hours, the suspension is filtered through celite and evaporated under reduced pressure to remove acetone. The residue is extracted twice with $Et_2O$, and the extract is then washed with saturated NaCl solution, 5% sodium bisulfite solution, and saturated NaCl solution. The organic phase is dried over $MgSO_4$, filtered, and evaporated to a solid 3.65 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 712.0 (46.6%) $M^+$.

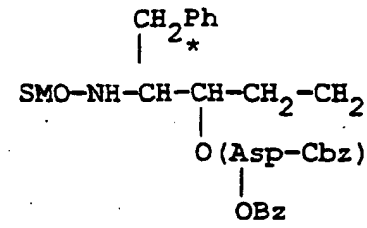
Step C: Preparation of 

(R isomer at *)

 , 3.52 g (4.95 mmol) is dissolved in 175 mL $CH_2Cl_2$, and cooled to 0°C. A solution of HOBT 0.7 g (5.19 mmol) in DMF is added, followed by DDC 1.07 g (5.19 mmol), and a solution of CAD 1.20 g (4.94 mmol) in 20 mL $CH_2Cl_2$/DMF. The mixture is stirred at room temperature overnight and is evaporated under reduced pressure to an oil with suspended solids. The mixture is suspended in $Et_2O$, filtered, and extracted with 1N citric acid, saturated NaCl solution, saturated $NaHCO_3$, and saturated NaCl solution. The organic phase is dried over $MgSO_4$, filtered, and evaporated to a white foam, 4.72 g. Chromatography on silica gel, eluting with a gradient of 25% to 50% EtOAc in Hexane gives the product as a solid, 3.43 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 937.4 (42.0%) $M^+$.

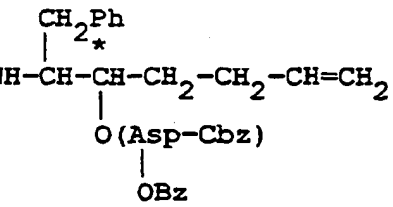
Step D: Preparation of 

(R isomer at *)

 , 3.44 g (3.63 mmol)

(R isomer at *)

is dissolved in THF, 20% Pd on carbon catalyst is added, and the suspension is pressurized to 50 psi with $H_2$ gas. After 18 hours the mixture is vented, filtered, and the filtrate is evaporated under reduced pressure to a grey foam. Chromatography on silica gel, eluting with MeOH/$CHCl_3$ (20/80) gives the product as a grey solid. The solid is dissolved in $CH_2Cl_2$, filtered through charcoal, and a solid is precipitated from the filtrate by addition of $Et_2O$. The solid is filtered, washed with $Et_2O$, and dried under reduced pressure to a white solid 0.88 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 713.4 (73.5%) $M^+$.

In a similar manner, 

(R isomer at *)

gives the S isomer.

**EXAMPLE 10**

**(Lys)O-$CH_2$-C(=O)-Phe-Alg-CAD·2HCl**

**Step A: Preparation of (Lys-2Boc)O-$CH_2$-C(=O)-Phe-Alg-CAD**

(Lys-2Boc)O-$CH_2$-$CO_2$H (Example Q) (1.30 g, 3.2 mmol) is dissolved in 10 mL of $CH_2Cl_2$ and cooled to 0°C, HOBT (433 mg, 3.2 mmol), DCC (661 mg, 3.2 mmol) and DMAP (195 mg, 1.60 mmol) are added sequentially. The white suspension is stirred for 15 minutes. Phe-Alg-CAD (Example N) (780 mg, 1.60 mmol) in 10 mL of dry $CH_2Cl_2$ is added dropwise and the reaction mixture is stirred at room temperature for 3 days. The reaction is filtered through Celite. The filtrate is washed with 1N HCl, saturated $NaHCO_3$, and brine. The organic phase is dried with $MgSO_4$ and concentrated under vacuum. The crude product is purified twice by silica gel chromatography with 1% MeOH/$CH_2Cl_2$ as eluent to give 610 mg of pure product; MS (FAB) 874 ($M^+$), 774, 674 (100%).

**Step B: Preparation of (Lys·2HCl)O-$CH_2$-C(=O)-Phe-Alg-CAD**

(Lys-2Boc)O-$CH_2$-C(=O)-Phe-Alg-CAD (100 mg, 0.11 mmol) is dissolved in 10 mL of dry $CH_2Cl_2$ and cooled to 0°C. Hydrogen chloride gas is passed through the reaction flask for 10 minutes and stirring is continued for 1 hour. A white precipitate appears and solvent is evaporated and the jelly residue is dissolved in $CH_2Cl_2$ and evaporated to dryness. The process is repeated several times to afford a white solid. It is washed with EtOAc/$Et_2O$ (1:2) and collected as fine white powder (58 mg).

HPLC showed 92% purity; MS (FAB) 675 (100% $M^+$ free base) 675 ($M^+-H_2O$).

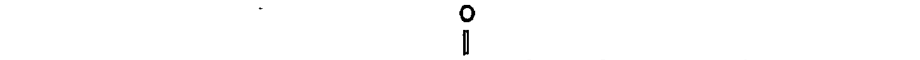
**EXAMPLE 11**

**(Asp)O-$CH_2$-C-Phe-Alg-CAD·HCl**

**Step A: Preparation of (Asp·Boc·t-Bu)O-$CH_2$-C-Phe-Alg-CAD**

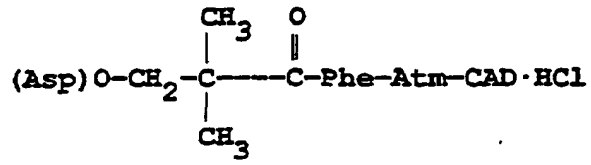
The (N-Boc-α-t-butylaspartyl) glycolate (1.01 g, 2.9 mmol) is dissolved in 10 mL of $CH_2Cl_2$. DCC (600 mg, 2.9 mmol), HOBT (393 mg, 2.9 mmol) and DMAP (178 mg, 1.46 mmol) are added sequentially to the reaction vessel at 0°C. After 15 minutes Phe-Alg-CAD (Example N) (850 mg, 1.74 mmol) in 10 mL of $CH_2Cl_2$ is added. The reaction mixture is stirred at room temperature for 2 days and worked up as usual. Silica gel chromatography with 1% to 2% MeOH/$CH_2Cl_2$ affords 760 mg of product as a white foam; MS (FAB) 818 ($M^+$ 48%), 762, 744, 718, 688, 644.

**Step B: Preparation of (Asp·HCl)O-$CH_2$-C-Phe-Alg-CAD·HCl**

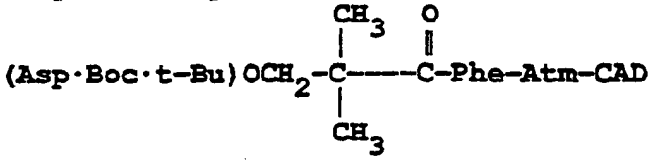


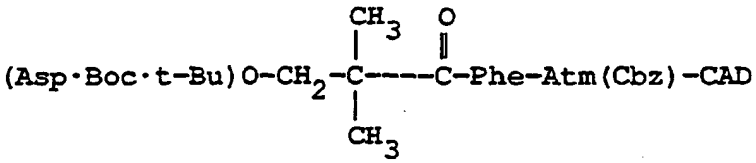
(Asp·Boc·t-Bu)O-$CH_2$-C-Phe-Alg-CAD (201 mg, 0.25 mmol) is dissolved in 20 mL of $CH_2Cl_2$. Hydrogen chloride gas is passed through the reaction mixture at 0°C for 15 minutes. The reaction is continuously stirred for 3 hours at room temperature. Solvent is removed and the residue is dissolved in fresh $CH_2Cl_2$ and evaporated. The process is repeated several times to afford a white solid which is washed with $Et_2O$/EtOAc and collected as a fine white powder (159 mg); MS (FAB) 661 ($M^+$ 91%) 643.

EXAMPLE 12



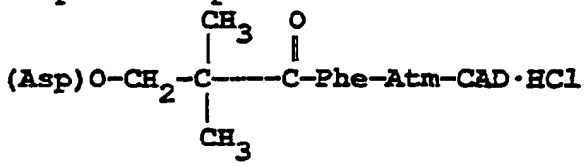
Step A: Preparation of

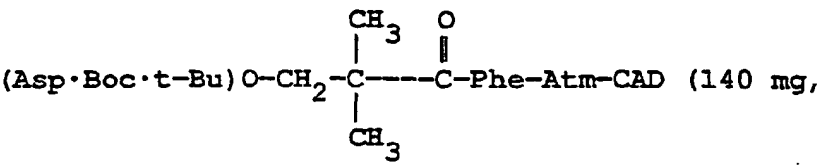




(373 mg, 0.35 mmol) (Example U) is dissolved in 25 mL of MeOH and 200 mg of TsOH (3 eq) and a catalytic amount of 20% palladium on carbon is added. The mixture is stirred under one atmosphere of hydrogen for 6 hours, filtered, and the solution neutralized with solid $NaHCO_3$. The MeOH is evaporated and the residue diluted with water and EtOAc. The mixture is extracted with EtOAc (3 x 30 mL) and dried (magnesium sulfate). The product is purified by chromatography with 3% MeOH:$CH_2Cl_2$ to afford 140 mg of product as a white foam; MS (FAB) 932 ($M^{+1}$).

Step B: Preparation of

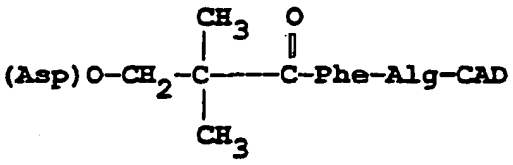




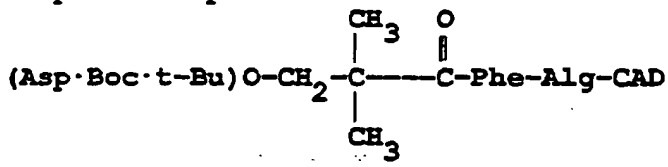
0.15 mmol) is dissolved in 10 mL of dry $CH_2Cl_2$, cooled to 0°C, and hydrogen chloride gas passed through for 1 hour, and the reaction stirred for 2 hours at room temperature. The solvent is

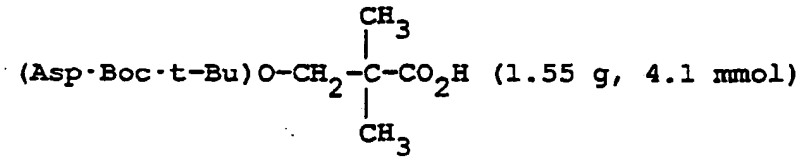
evaporated and the residue treated with $CH_2Cl_2$ and evaporated. The yellow solid is collected by filtration. The filter cake is washed many times with EtOAc and dried under vacuum; MS (FAB) 776 ($M^{+1}$), 758 ($M^{-18}$).

**EXAMPLE 13**



**Step A: Preparation of**





(Example S, Step B acid before coupling to Phe-O-Bz is used) is dissolved in 70 mL of $CH_2Cl_2$ cooled to 0°C, DCC (933 mg, 4.52 mmol), HOBT (610 mg, 4.52 mmol), DMAP (250 mg, 2.05 mmol), and Phe-Alg-CAD (1.0 g, 2.01 mmol) (Example N) are added. The mixture is stirred at room temperature for 2 days, filtered, and the solution washed with 1N HCl, saturated $NaHCO_3$, NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 2% MeOH:$CH_2Cl_2$ to afford 1.3 g of the product as a white foam. MS (FAB) 859 ($M^{+1}$).

**Step B: Preparation of (Asp)O-$CH_2$-C(CH$_3$)(CH$_3$)-C(=O)-C-Phe-Alg-CAD**

(Asp·Boc·t-Bu)O-$CH_2$-C(CH$_3$)(CH$_3$)-C(=O)-C-Phe-Alg-CAD (196 mg, 0.23 mmol) is dissolved in 15 mL of $CH_2Cl_2$. Hydrogen chloride gas is passed through the solution for about 30 minutes at 0°C and the mixture stirred at 0°C to room temperature for a total of 3 hours. The $CH_2Cl_2$ is evaporated and the residue rinsed with $CH_2Cl_2$ several times and the white solid collected by filtration and washed with EtOAc/$Et_2O$ to afford 143 mg of the product as a white powder; MS (FAB) 702 ($M^{+1}$) 685 ($m^{-18+1}$).

## PREPARATION OF STARTING MATERIALS

### EXAMPLE A

### Cbz-Ser-CAD

Cbz-Ser (500 mg, 2.09 mmol) is stirred in $CH_2Cl_2$ (30 mL) and DMF (10 mL) at 0°C and DCC (474 mg, 2.30 mmol, 1.1 eq), CAD (534 mg, 2.19 mmol, 1.05 eq) and HOBT (310 mg, 2.30 mmol, 1.1 eq) is added. The mixture is stirred for 2 days, filtered and evaporated. The residue is taken up in ethyl acetate (50 mL) and washed with 2 N $Na_2CO_3$ (75 mL), brine (75 mL), dried ($MgSO_4$), filtered and evaporated to afford an off-white solid. This is purified by column chromatography on silica gel eluting with 2%, 3% then 4% methanol/$CH_2Cl_2$ to give 600 mg of a white solid. A portion (100 mg) is recrystallized from chloroform to give 67 mg of a white solid; mp 144-146°C.

**EXAMPLE B**

**Ser-CAD**

Cbz-Ser-CAD (Example A) (6.8 g, 14.6 mmol) in EtOH (100 mL) with 20% palladium on carbon (0.5 g) is shaken under $H_2$ at 50 pounds per square inch (psi) at room temperature for 1 hour. The mixture is filtered and evaporated to leave a white foam. This is recrystallized from ethyl acetate to give 4.03 g of a fluffy white solid. Additional product (406 mg) is obtained from the mother liquors on standing; MS (FAB) 331.2 (100%).

**EXAMPLE C**

**SMO-Phe-Ser-CAD**

A mixture of SMO-Phe (European Published Application EP 0399,556) (1.90 g, 6.06 mmol, 1.0 eq), Ser-CAD (Example B) (6.06 mmol, 2.0 g, 1.0 eq), DCC (1.37 g, 6.66 mmol, 1.1 eq) and HOBT (0.90 g, 6.66 mmol, 1.1 eq) is stirred in $CH_2Cl_2$ (100 mL) and DMF (50 mL) at room temperature under $N_2$ for 3 days. The solvents are evaporated and the residue taken up in ethyl acetate (200 mL). This is washed with 2 N $Na_2CO_3$ (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and evaporated to afford a white foam. This is purified by column chromatography on silica gel eluting with 3% then 4% MeOH/$CH_2Cl_2$ to give a white foam; mp 99-102°C.

**EXAMPLE D**

**SMO-Phe-Thr-CAD**

**Step A: Preparation of SMO-Phe-Thr**

A mixture of SMO-Phe (European Published Application EP 0399,556) (16.6 g, 53 mmol) and HOBT (7.83 g, 58 mmol, 1.1 eq) in dichloromethane (400 mL) and dimethylformamide (50 mL) is cooled to 0°C under nitrogen. Threonine benzyl ester, hydrochloride (13.6 g, 55 mmol, 1.05 eq), triethylamine (8.06 mL,

58 mmol, 1.1 eq) and DCC (12.03 g, 58 mmol, 1.1 eq) are added and the mixture stirred at 0°C for 1 hour. After warming to room temperature, the mixture is filtered and evaporated. The residue is partitioned between ethyl acetate and water, the organic layer separated, washed with 2N sodium bicarbonate, brine, dried ($MgSO_4$), filtered, and evaporated. The residue is purified by column chromatography on silica gel eluting with dichloromethane then 4% methanol/dichloromethane to afford 19 g of a solid. This is dissolved in methanol (300 mL) and 5% palladium on carbon (1.9 g) added. The mixture is stirred vigorously under hydrogen at room temperature for 5 hours. The mixture is filtered and evaporated to leave 14.8 g of a white solid; $^1H$ NMR (90 MHz, $CDCl_3$ + $d^6$-DMSO) δ 7.10-7.50 (5H, m), 6.29 (1H, d, J 10.2Hz), 5.49 (3H, br. s), 3.90-4.55 (3H, m), 3.30-3.50 (4H, m), 2.75-3.10 (6H, m) and 1.15 (3H, d, J 6.6Hz).

**Step B: Preparation of SMO-Phe-Thr-CAD**

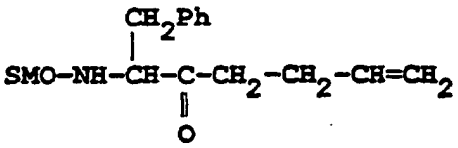
SMO-Phe-Thr (3.98 g, 9.57 mmol) is stirred at 0°C in DMF (30 mL) and dichloromethane (120 mL) and DCC (2.17 g, 10.5 mmol, 1.1 eq), HOBT (1.42 g, 10.5 mmol, 1.1 eq) and CAD (2.44 g, 10.1 mmol, 1.05 eq) added. The mixture is stirred at room temperature under nitrogen for 2 days and filtered. The filtrate is washed with 2N sodium carbonate (2 x 100 mL), brine (100 mL), dried ($MgSO_4$), filtered, and evaporated to leave an oily foam. This is purified by column chromatography on silica gel, eluting with 2% methanol/dichloromethane to give a white foam. This is crystallized from dichloromethane to give 2.41 g of a fluffy white solid; MS (FAB) 641.6 (51.3%) $(M+H)^+$.

**EXAMPLE E**

**SMO-Phe-N($CH_3$)$OCH_3$**

A solution of 8.0 g (25.4 mmol) of SMO-Phe (European Published Application EP 0399,556) in 100 mL of THF/$CH_2Cl_2$ (1/1) is cooled to -40°C and 4.54 g (28 mmol) of carbonyldiimidazole added. The mixture is then kept at -5°C for 1.5 hours. To this is added a solution of 2.73 g (28 mmol) of O,N-dimethylhydroxylamine, hydrochloride, and 3.23 mL (28 mmol) of N-methylpiperidine in 40 mL $CH_2Cl_2$. After stirring at room temperature overnight, the mixture is filtered and the filtrate evaporated. The residue is taken up in EtOAc and washed with 1 N citric acid, saturated NaCl, saturated $NaHCO_3$, and saturated NaCl. Drying over $MgSO_4$ and removal of the solvent under reduced pressure leaves 9.69 g of the crude product. Chromatography on silica gel, eluting with EtOAc/$CHCl_3$/MeOH (49/49/2) gives 7.56 g of the product as a syrup which solidifies. The structure is confirmed by NMR and mass spectroscopy; MS (FAB) 358.1 (100%) $M^+$.

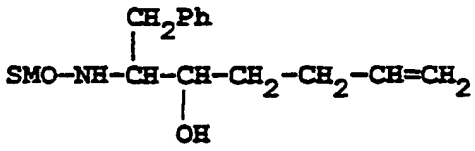
**EXAMPLE F**



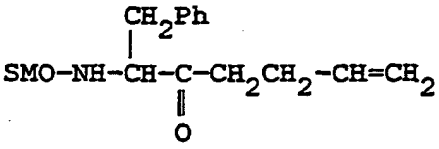
Under nitrogen, a Grignard solution prepared from 5.44 g (224 mmol) of Mg turnings and 22.7 mL (224 mmol) of 4-bromo-1-butene in 350 mL THF is heated to reflux, then cooled to -5°C and treated with a suspension of 20.0 g (55.9 mmol) of SMO-Phe-N($CH_3$)$OCH_3$ (Example E) in 135 mL THF. After stirring at room temperature overnight, the mixture is evaporated to an oil. The oil is poured into a cold, saturated solution of $NH_4Cl$ and extracted with EtOAc. The EtOAc is washed with 1 N citric acid, saturated

NaCl, saturated $NaHCO_3$, and saturated NaCl. Drying over $MgSO_4$ and removal of the solvent under reduced pressure gives the crude product as an oil. Chromatography on silica gel, eluting with hexane/EtOAc (70/30) gives 16.9 g of the product as an oil. The structure is confirmed by NMR and Mass Spectroscopy; MS (EI) 353.28 $M^+$.

**EXAMPLE G**

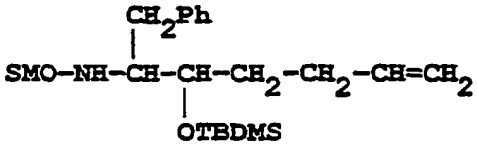


A solution of 6.35 g (18.0 mmol) of

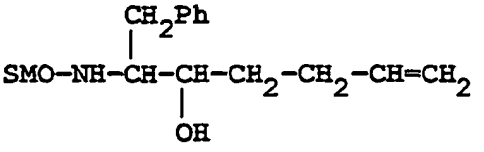


(Example F) in 200 mL of absolute EtOH is treated with 3.89 g (72.0 mmol) of $KBH_4$ followed by 20 mL of $H_2O$. After stirring at room temperature for 2.5 hours, 100 mL of acetone is added and the mixture stirred for 15 minutes. The suspension is filtered and the filtrate evaporated to an oil which solidifies. There is obtained 6.04 g of the product. The structure is confirmed by NMR and Mass Spectroscopy; MS (EI) 355.25 (3.8%) $M^+$.

**EXAMPLE H**



A solution of 5.95 g (16.8 mmol) of

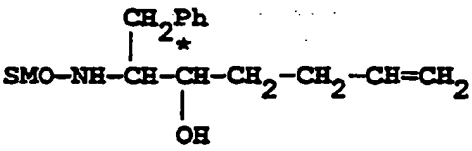


(Example G) in 100 mL THF

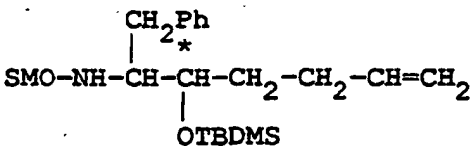
is treated with 1.48 g (22 mmol) of imidazole and 3.29 g (22 mmol) of t-butyldimethylsilyl chloride and the mixture stirred at room temperature for 2 days. An additional 0.8 g (11.8 mmol) of imidazole and 1.77 g (11.7 mmol) of t-butyldimethylsilyl chloride is then added and the mixture stirred overnight. The solvent is removed under reduced pressure and the residue suspended in EtOAc/$Et_2O$ (1/1) and washed with $H_2O$, 1 N citric acid, saturated NaCl, saturated $NaHCO_3$, and saturated NaCl. Drying over $MgSO_4$ and removal of the solvent under reduced pressure gives the crude product as a mixture of diastereomers. Chromatography on silica gel, eluting with a gradient of 0% to 20% EtOAc in hexane gives 3.34 g of the faster eluting diastereomer as a glass. The structure is confirmed by NMR and Mass Spectroscopy; MS (EI) 469 (100%) $M^+$.

Continued elution from the column gives 2.86 g of the slower eluting diastereomer as a glass. The structure is confirmed by NMR and Mass Spectroscopy; MS (EI) 469 (100%) $M^+$.

**EXAMPLE I**



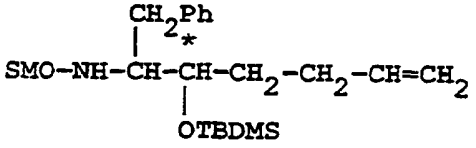
**SMO-NH-CH(CH$_2$Ph)-CH(OH)-CH$_2$-CH$_2$-CH=CH$_2$ (Separate isomers, R and S at *)**



SMO-NH-CH(CH$_2$Ph)-CH(OTBDMS)-CH$_2$-CH$_2$-CH=CH$_2$ (derived from the faster eluting R isomer at *) (Example H) 9.02 g (18.5 mmol) is dissolved in 350 mL anhydrous THF to which a solution of tetrabutylammonium fluoride (1 M in THF), 80 mL is added. After stirring at 25°C for 3 hours, the mixture is evaporated under reduced pressure to

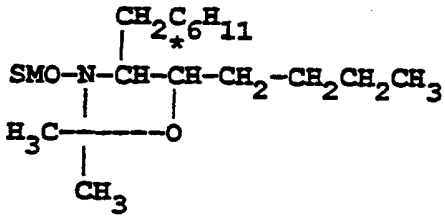
an oil. The oil is suspended in $Et_2O$ and extracted with 1 N citric acid, saturated NaCl solution, saturated $NaHCO_3$ solution and saturated NaCl solution. The organic phase is dried over anhydrous $MgSO_4$, filtered and evaporated to a crude oil, 9 g in weight. The oil is crystallized from a mixture of $Et_2O$/hexane (10/90) giving a white solid, 5.55 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 355.3 (100%) $M^+$.

In an identical manner, 7.2 g (14.8 mmol) of

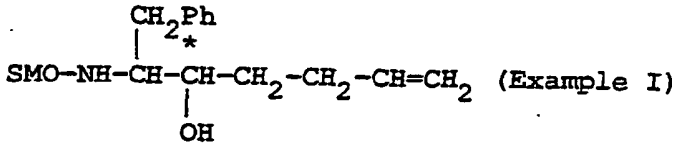


(derived from the slower eluting S isomer at *) (Example H) yields 4.79 g of the corresponding S isomer product as a white solid. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 355.3 (100%) $M^+$.

**EXAMPLE J**



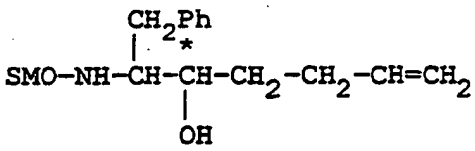
at *)



(R isomer at *), 0.50 g (1.41 mmol) is dissolved in 40 mL of 2,2-dimethoxypropane and heated to 50°C. A trace of anhydrous p-toluenesulfonic acid is added, and the mixture is stirred for 1.25 hours. The mixture is evaporated under reduced pressure and saturated $NaHCO_3$ solution is added to the residue. The oily suspension is extracted into $Et_2O$, washed with saturated NaCl solution and is evaporated to an

oil. Chromatography on silica gel, eluting with Hexane/EtOAc (5/95) gives 0.35 g of an oil. The oil is dissolved in 75 mL isopropanol and 10% Rhodium on carbon catalyst, 0.5 g is added. The mixture is placed under $H_2$ gas at 50 psi for 30 hours, filtered to remove the catalyst, and evaporated under reduced pressure. The residue is resuspended in 2,2-dimethoxypropane and a trace of p-toluenesulfonic acid is added. The mixture is heated to 50°C for 1 hour, and evaporated under reduced pressure. The residue is suspended in saturated $NaHCO_3$ solution, extracted into $Et_2O$, washed with saturated NaCl solution, and evaporated to an oil. Chromatography on silica gel, eluting with EtOAc/Hexane (25/75) gives the product as an oil, 0.18 g. NMR spectroscopy confirms R stereochemistry at *, and Mass Spectroscopy further confirms the structure; MS (EI) 403 (17.5%) $M^+$.

In a similar manner, 0.50 g (1.41 mmoles) of



(S isomer at *) gives the S isomer product as an oil, 0.18 g. NMR spectroscopy confirms the structure and the S stereochemistry at *. Mass Spectroscopy further confirms the structure; MS (EI) 403 (15.4%) $M^+$.

**EXAMPLE K**

**Boc-Alg-CAD**

To a solution of Boc-Alg (7.36 g, 34.23 mmol) in 200 mL of dry $CH_2Cl_2$ at 0°C are added DCC (8.48 g, 41.10 mmol), DMAP (2.5 g, 20.49 mmol) and HOBT (5.55 g, 41.07 mmol). The resulting white suspension is stirred for 15 minutes. CAD (8.32 g, 34.23 mmol) is dissolved in 100 mL of dry $Et_2O$ and added to the

reaction mixture dropwise through an addition funnel. After stirring at room temperature overnight, the reaction mixture is filtered and the white solid washed with $CH_2Cl_2$ thoroughly. The filtrate is evaporated and the residue taken up in 500 mL of EtOAc and washed with 1N HCl, saturated $NaHCO_3$, and dried ($MgSO_4$). Solvent is removed and the residue purified by silica gel chromatography with 20% EtOAc/hexane to give 13.0 g of the product as a white solid; MS (FAB) 441 ($M^+$), 385, 341.

**EXAMPLE L**

**Alg-CAD**

Boc-Alg-CAD (Example K) (1.01 g, 2.29 mmol) is dissolved in 100 mL of dry $CH_2Cl_2$. Hydrogen chloride gas is passed through this solution for 10 minutes. The reaction mixture is stirred for 3 hours. Solvent is removed and the residue dissolved in $H_2O$ (50 mL). The aqueous solution is extracted with $Et_2O$ (50 mL x 2). The aqueous layer is then basified to pH 14 with NaOH pellets. The cloudy solution is extracted with EtOAc/$Et_2O$ (100 mL x 3). The organic layer is dried with $MgSO_4$. Solvent is removed under reduced pressure to afford a white solid (760 mg); $^1H$ NMR ($CDCl_3$ + $D_2O$) 7.5 (br d, 1H), 5.7 (m, 1H), 5.15 (m, 2H), 4.31 (m, 1H), 3.6 (m, 1H), 3.2 (br m, 2H), 2.5 (m, 2H), 1.9 (m, 1H), 1.8-1.1 (m, 14H), 0.95 (d, 3H), 0.93 (d, 3H).

**EXAMPLE M**

**Boc-Phe-Alg-CAD**

To a solution of Boc-Phe (5.8 g, 21.89 mmol) in 200 mL of $CH_2Cl_2$ at 0°C is added sequentially DMAP (1.12 g, 9.18 mmol), HOBT (3.7 g, 27.38 mmol) and DCC (5.27 g, 25.54 mmol). The resulting white suspension is stirred for 15 minutes. A solution of Alg-CAD (Example L) (6.2 g, 18.23 mmol) in 100 mL of $CH_2Cl_2$

is added to the reaction mixture through an addition funnel. The reaction mixture is stirred vigorously at room temperature overnight. The white solid is filtered and the filtrate washed with 1 N HCl, saturated $NaHCO_3$, and brine. The organic solution is dried ($MgSO_4$) and concentrated and further purified by silica gel chromatography to give a white solid (7.1 g); MS (FAB) 589 ($M^+$ +1) 514.

**EXAMPLE N**

**Phe-Alg-CAD**

Boc-Phe-Alg-CAD (Example M) (7.0 g, 11.92 mmol) is dissolved in 500 mL of $CH_2Cl_2$ with the aid of a few drops of MeOH. Dry HCl gas is passed through solution for 15 minutes and the reaction mixture is further stirred for another 3 hours. Solvent is evaporated and the residue dissolved in $H_2O$ (200 mL). It is then extracted with $CH_2Cl_2$ (3 x 250 mL). The aqueous layer is basified with NaOH pellets and extracted with $CH_2Cl_2$ (3 x 300 mL). The combined extracts are dried ($MgSO_4$) and evaporated to give 5.70 g of white solid; MS (FAB) 489 ($M^+$ +1) 471 ($M^+-H_2O$).

**EXAMPLE O**

**$TBDMSOCH_2$-C-Phe-Alg-CAD**

$TBDMSOCH_2CO_2H$ (1.05 g, 5.53 mmol) is dissolved in 15 mL of dry $CH_2Cl_2$ at 0°C. HOBT (824 mg, 6.10 mmol), DMAP (338 mg, 2.72 mmol), and DCC (11.26 g, 6.10 mmol) are added. After 15 minutes, a solution of Phe-Alg-CAD (Example N) in 15 mL of $CH_2Cl_2$ is added slowly. Reaction mixture is stirred at room temperature overnight. Dicyclohexylurea is filtered and the filtrate washed with 1N HCl, saturated $NaHCO_3$, and dried with $MgSO_4$. The solvent is removed and the residue chromatographed with 2%

MeOH/$CH_2Cl_2$ to give 1.0 g of product as a white foam; MS (FAB) 659 ($M^+$) 602.

**EXAMPLE P**

$HO-CH_2-C(=O)-Phe-Alg-CAD$



$TBDMSOCH_2-C(=O)-Phe-Alg-CAD$ (Example O) (700 mg, 1.06 mmol) is dissolved in 15 mL of MeOH. A catalytic amount of para-toluenesulfonic acid is added and the reaction mixture heated to 78°C for 1 hour. The methanol is evaporated and the residue chromatographed over silica gel with 2% to 3% MeOH/$CH_2Cl_2$ to give the product as a white foam (325 mg). A portion of the product is recrystallized from MeOH/EtOAc/hexane to give 16 mg of white powder; mp 185-187°C; MS (FAB) 546 ($M^+$), 528 ($M^+-H_2O$).

**EXAMPLE Q**

**(Lys-2Boc)O-$CH_2$-$CO_2H$**

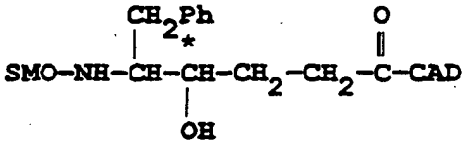
**Step A: Preparation of (Lys-2Boc)O-$CH_2$-$CO_2Bz$**

Carbonyldiimidazole (2.25 g, 13.88 mmol) is added to the solution of Bis-Boc Lysine (4.00 g, 11.56 mmol) in 40 mL of THF at 0°C followed by a catalytic amount of DMAP. After 10 minutes, benzyl glycolate (1.28 g, 7.7 mmol) is added and the solution refluxed overnight. The solvent is evaporated and the residue taken up in 300 mL EtOAc. It is washed with 1N HCl and with saturated $NaHCO_3$. The organic phase is dried with $MgSO_4$ and concentrated. The crude reaction product is chromatographed with 15% EtOAc/hexane on silica gel to give 3.6 g of product as a colorless oil; MS (FAB) 495 ($M^+$) 439, 395.

**Step B: Preparation of (Lys-2Boc)O-$CH_2$-$CO_2H$**

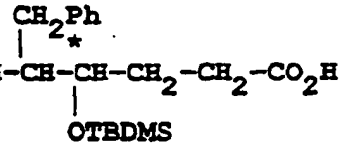
(Lys-2Boc)O-$CH_2CO_2Bz$ (4.90 g, 9.9 mmol) is dissolved in 100 mL of EtOAc and 0.5 g of 20% palladium on carbon is added. The hydrogenolysis is carried out under 50 psi until all the starting material is consumed. The catalyst is filtered and washed thoroughly with EtOAc. Solvent is removed to leave a viscous gel (3.80 g); MS chemical ionization (CI), 408 ($M^+$+1).

**EXAMPLE R**

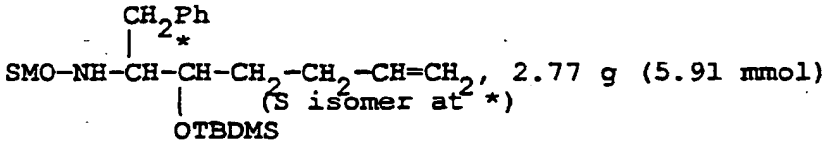


**(S isomer at *)**

**Step A: Preparation of**

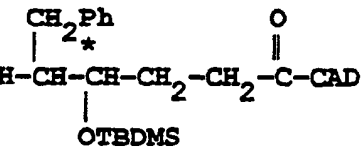


**(S isomer at *)**

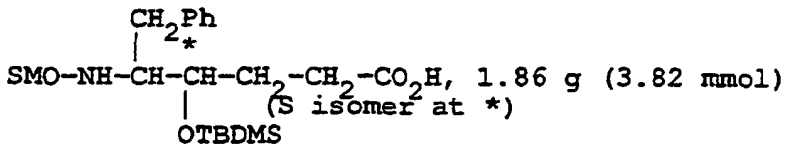


(Example H) is dissolved in 140 mL acetone and cooled to 15°C. $NaIO_4$ 9.50 g (44.41 mmol) and $RuO_2xH_2O$, 0.10 g are dissolved in 60 mL $H_2O$ and added to the previously described solution, giving an exotherm which is controlled at 20°C by external cooling over 2 hours. Isopropanol, 30 mL is added to the mixture followed by filtration through celite. The filtrate is evaporated under reduced pressure and the residue is saturated with solid $NaHCO_3$. The mixture is extracted exhaustively with $CHCl_3$ which is washed with 4% $NaSO_3$ solution buffered to pH 2 with concentrated HCl. The organic phase is washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated to a solid, 2.51 g. The solid is

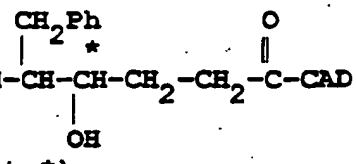
filtered through silica gel eluted with MeOH:$CHCl_3$ (10:90). Recrystallization from hexane gives a solid, 1.95 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS ($El^+$) 487.25 (100.0%) $M^+$.

**Step B: Preparation of** 

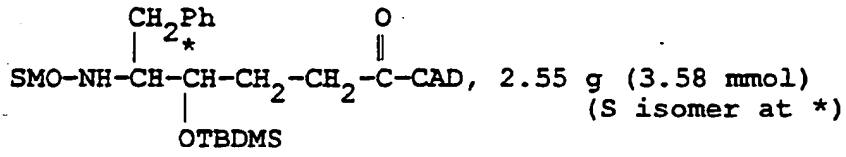
**(S isomer at *)**



and HOBT 0.53 g (3.94 mmol) is dissolved in 5 mL DMF, diluted to 80 mL with $CH_2Cl_2$, and cooled to 0°C. DCC, 0.81 g (3.79 mmol) is added, followed by a solution of CAD 0.93 g (3.82 mmol) in 25 mL $CH_2Cl_2$/DMF. The mixture is stirred at room temperature overnight and is evaporated under reduced pressure to an oil with suspended solids. The mixture is suspended in EtOAc, filtered, and extracted with 1N citric acid, saturated NaCl solution, saturated $NaHCO_3$, and saturated NaCl solution. The organic phase is dried over $MgSO_4$, filtered, and evaporated to an oil with suspended solids. The residue is suspended in $Et_2O$, filtered, and evaporated under reduced pressure to a solid, 2.76 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 712.2 (100.0%) $M^+$.

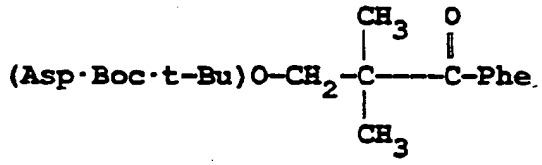
**Step C: Preparation of** 

**(S isomer at *)**

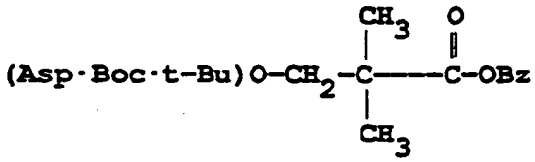


is dissolved in 70 mL 1 M t-butyl ammonium fluoride in THF. After stirring at 25°C for 6 hours, the mixture is evaporated under reduced pressure to an oil. The oil is suspended in 125 mL EtOAc and washed three times with 75 mL 1N HCl, three times with saturated $NaHCO_3$, and saturated NaCl. The organic phase is dried over $MgSO_4$, filtered, and evaporated to a solid 2.25 g. The solid is recrystallized from a mixture of $CH_2Cl_2$ and $Et_2O$, and dried under reduced pressure to a solid, 0.75 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 598.2 (100.0%) $M^+$.

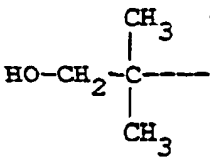
**EXAMPLE S**



**Step A: Preparation of**

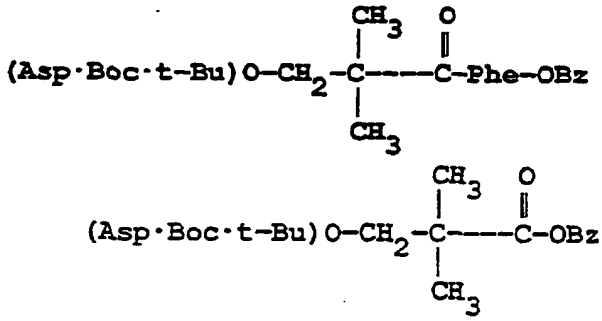


N-Boc·Asp·O-t-Bu (17.1 g, 53 mmol), freed from the dicyclohexylamine salt by treatment with citric acid is dissolved in 300 mL of THF and cooled to 0°C. CDI (8.6 g), the alcohol



(11.09, 1.0 eq), and a catalytic amount of DMAP are added and the mixture stirred at 0°C for 30 minutes and then refluxed for 24 hours. After cooling to room temperature, THF is removed by rotatory evaporation, and the residue dissolved in EtOAc and washed sequentially with 1N HCl, saturated solution of $NaHCO_3$, and NaCl, and dried (magnesium sulfate). The crude product is purified by chromatography with 10% to 20% EtOAc-hexane to afford 12.1 g of a white solid; MS (FAB) 367 ($M^{-2}$ t-$Bu^{+1}$) 324 (100%, M-Boc-t-$Bu^{+1}$).

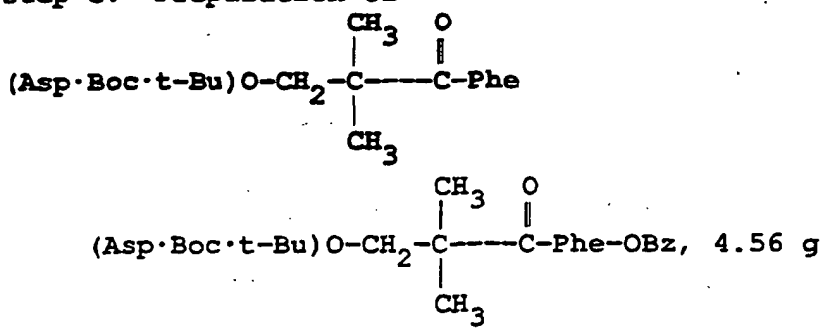
**Step B: Preparation of**



(16.7 mmol) is dissolved in 100 mL of EtOAc and a catalytic amount of 20% palladium on carbon is added and the mixture is stirred under one atmosphere of hydrogen for 2 hours. The mixture is filtered through celite, washed with EtOAc, and evaporated to dryness to afford an oil (~8.0 g). The crude product is dissolved in 70 mL of $CH_2Cl_2$, DCC (3.90 g, 1.1 eq), HOBT (2.5 g, 1.1 eq), DMAP (1.0 g, 0.5 eq), are added followed by Phe-OBz (from 5.0 g, 17.1 mmol of Phe-OBz·HCl). The mixture is stirred at room temperature overnight, DCU filtered, and the solution is washed with 1N HCl, saturated solution of $NaHCO_3$, NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 1% MeOH:$CH_2Cl_2$ to

afford 11.4 g of a white solid; MS (FAB) 527 ($M-Boc^{+1}$) 471 ($M-Boc-t-Bu^{+1}$).

**Step C: Preparation of**



(Asp·Boc·t-Bu)O-$CH_2$-C(-$CH_3$)(-$CH_3$)-C(=O)-Phe-OBz, 4.56 g

(7.27 mmol) is dissolved in 80 mL of EtOAc and a catalytic amount of 20% palladium on carbon is added and the mixture stirred under one atmosphere of hydrogen for 4 hours. The mixture is filtered through celite, the solvent evaporated, and the product used without further purification.

## EXAMPLE T

## Atm(Cbz)-CAD

**Step A: Boc-Atm(Cbz)-CAD**

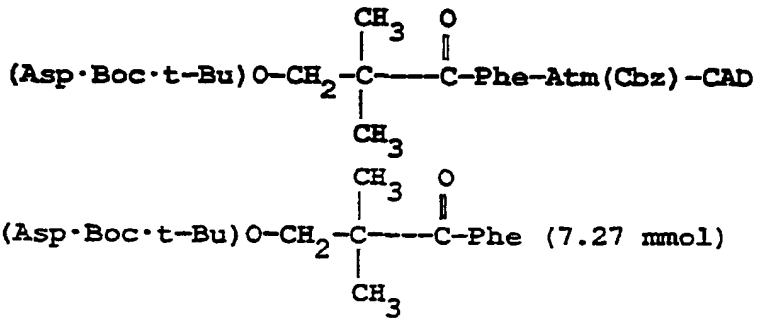
A mixture of Boc-Atm(Cbz) (European Published Patent Application EP0399,556), 6.3 g (14.9 mmol), CAD, 4.0 g (1.1 eq), DCC, 3.4 g (1.1 eq), HOBT, 2.2 g (1.1 eq), in 50 mL of DMF is stirred at room temperature overnight. The DCU is filtered and DMF removed under vacuum. The residue is taken up in 300 mL of EtOAc, washed with 1N citric acid, saturated solution of $NaHCO_3$, NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 1% MeOH:$CH_2Cl_2$ to afford 4.22 g of product as a white foam and a second portion of 7.5 g of product; MS (FAB) 647 ($M^+$).

**Step B: Atm(Cbz)-CAD**

Boc-Atm(Cbz)-CAD, 2.5 g (3.86 mmol) is dissolved in 40 mL of $CH_2Cl_2$ and 3 mL of MeOH to afford a clear

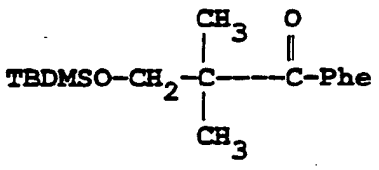
solution. Hydrogen chloride gas is passed through the solution for 10 minutes, and the reaction stirred for another 3.5 hours. The solvent is removed and the residue dissolved in 100 mL of EtOAc and 100 mL of $NaHCO_3$. The layers are separated and the EtOAc layer is washed with NaCl and dried (magnesium sulfate). The solvent is evaporated to afford 2.2 g of product as a pale white foam which is used without further purification.

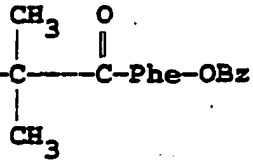
**EXAMPLE U**



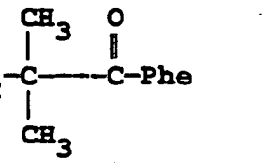

(Example S) is dissolved in 100 mL of DMF at 0°C and Atm(Cbz)-CAD (3.4 g, 6.1 mmol) (Example T), DCC (1.51 g, 7.32 mmol), and HOBT (1.0 g, 7.31 mmol) are added. The mixture is stirred at room temperature overnight. The DCU is filtered, DMF is removed by rotatory evaporation, and the residue is dissolved in 200 mL of EtOAc, washed with 1N citric acid, saturated solution of $NaHCO_3$ and NaCl, and dried (magnesium sulfate). The product is purified by repeated chromatography (4X) with 1% MeOH:$CH_2Cl_2$ to afford 4.6 g of a yellowish foam; MS (FAB) 1066 $(M^{+1})^+$.

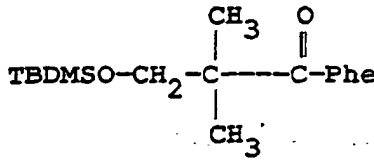
**EXAMPLE V**



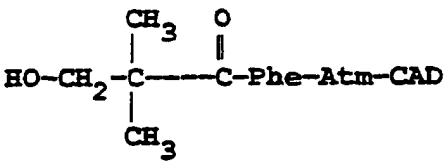
**Step A: Preparation of** 

A mixture  (4.20 g, 18 mmol), Phe-OBz (from 5.0 g, 17.1 mmol of Phe-OBz·HCl), DCC (3.9 g, 1.1 eq), HOBT (2.5 g, 1.1 eq), DMAP (1.0 g, 0.5 eq) is dissolved in 200 mL of $CH_2Cl_2$. The mixture is stirred at room temperature overnight, filtered, and the solution washed with 1N HCl, saturated $NaHCO_3$ and NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 15% EtOAc:hexane to afford 6.94 g of the product as a clear oil; MS (FAB) 470 ($M^+$).

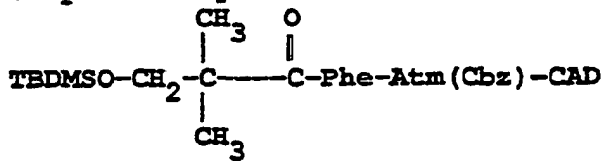
**Step B: Preparation of** 

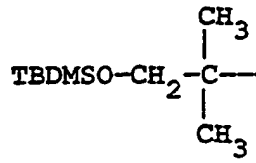
 (2.0 g, 4.2 mmol) is dissolved in 50 mL of EtOAc and a catalytic amount of 20% palladium on carbon is added and the mixture stirred under one atmosphere of hydrogen for 2 hours. The mixture is filtered, the solvent evaporated to afford 1.7 g of product which is used without further purification.

**EXAMPLE W**



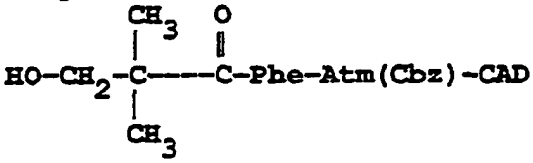
**Step A: Preparation of**

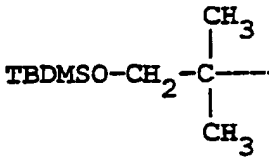




Atm(Cbz)-CAD (1.0 eq) (Example T) are dissolved in 50 mL of DMF, cooled to 0°C, and DCC (960 mg, 1.2 eq) and HOBT (580 mg, 1.2 eq) added. The mixture is stirred at room temperature overnight, filtered, and DMF removed by rotatory evaporation. The residue is dissolved in 100 mL of EtOAc and washed with 1N citric acid, saturated $NaHCO_3$ and NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 1% to 2% MeOH:$CH_2Cl_2$ to afford 1.6 g of product as a white foam; MS (FAB) 908 ($M^+$).

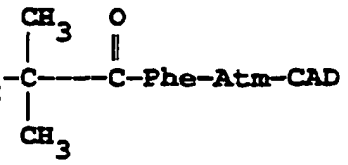
**Step B: Preparation of**

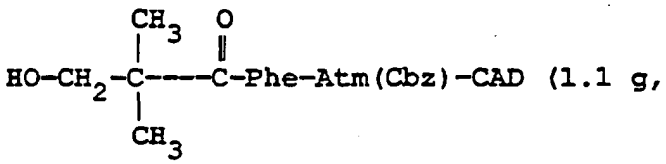




0.37 mmol) is dissolved in 15 mL of MeOH and a catalytic amount of TsOH is added. The reaction mixture is heated to 60°C for 3 hours, MeOH evaporated, and the residue taken up into water and EtOAc, and extracted with EtOAc (3 x 30 mL), and

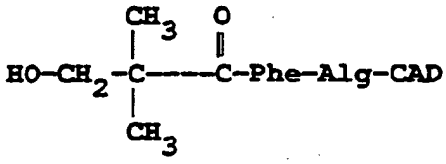
dried (magnesium sulfate). The product is purified by chromatography with 2% MeOH:$CH_2Cl_2$ to afford 280 mg of the product as a white foam; MS (FAB) 795 ($M^{+1}$).

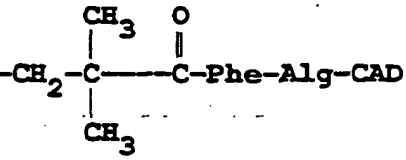
**Step C: Preparation of** 

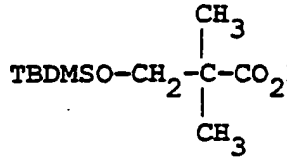


1.38 mmol) is dissolved in 20 mL of dry MeOH. TsOH (530 mg, 0.2 eq) and a catalytic amount of 10% palladium on carbon are added and the mixture stirred under one atmosphere of hydrogen at room temperature for 24 hours. The mixture is filtered and the solvent evaporated. The product is purified by chromatography with 3% to 5% MeOH:$CH_2Cl_2$ to afford 700 mg of product as a light yellow foam; MS (CI) 660 ($M^+$).

**EXAMPLE X**

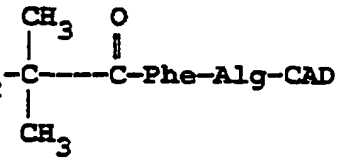


**Step A: Preparation of** 



Phe-Alg-CAD (1.00 g, 2.05 mmol) (Example N), DCC (907 mg, 4.40 mmol), HOBT (594 mg, 4.4 mmol), and DMAP (268 mg, 220 mmol) are dissolved in 20 mL of

$CH_2Cl_2$. The mixture is stirred at 0°C to room temperature for 40 hours, filtered, washed with 1N HCl, $NaHCO_3$, NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 1% to 2% MeOH:$CH_2Cl_2$ to afford 838 mg of the product as a white foam; MS (FAB) 702 ($M^+$) 684 ($M^{+-18}$).

**Step B: Preparation of** 

TBDMSO-$CH_2$-C(CH$_3$)(CH$_3$)-C(=O)-Phe-Alg-CAD (800 mg, 1.14 mmol) is dissolved in 15 mL of MeOH. A catalytic amount of TsOH is added and the mixture heated to reflux for 2 hours. The MeOH is removed by rotatory evaporation. The product is purified by chromatography with 2% to 3% MeOH:$CH_2Cl_2$ to afford 523 mg of the product as a white foam; MS (FAB) 588 ($M^+$) 570 ($m^{+-18}$).

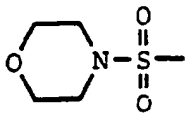
CLAIMS

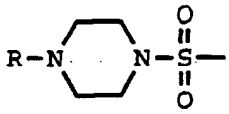
1. A compound of Formula I

A-E-G-J

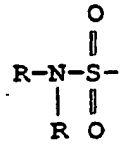
I

wherein A is

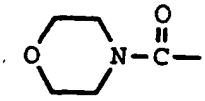


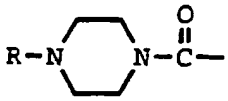


wherein R is hydrogen or alkyl of from one to six carbon atoms,

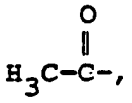


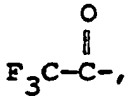
, wherein R is as defined above,

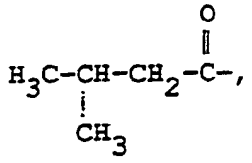


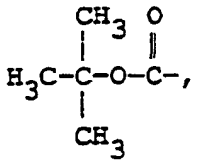


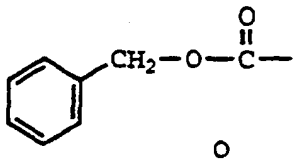
wherein R is as defined above,

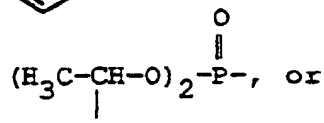


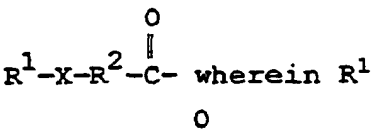


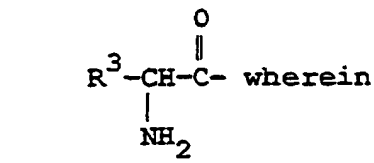


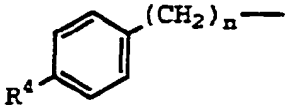










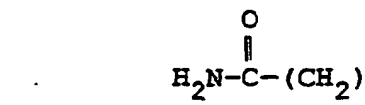


wherein n is zero or an integer of 1 or 2 and $R^4$ is hydrogen or hydroxyl,

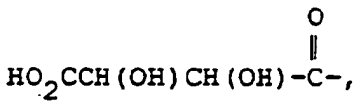
$CH_3-$,

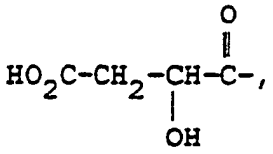
$H_2N-(CH_2)_4-$,

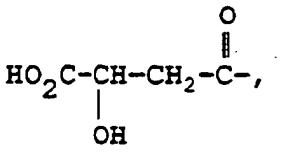
$HO_2C-(CH_2)_m-$ wherein m is an integer of 1 or 2, or

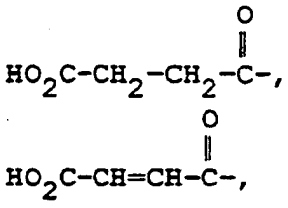


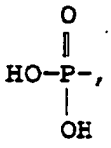
above,

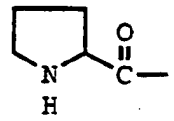


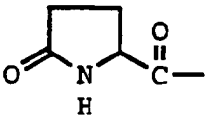






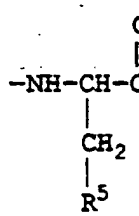


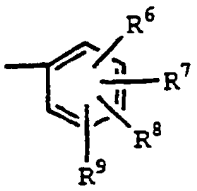




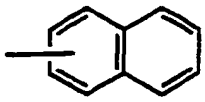
X is O, S, or NH, and

$R^2$ is alkyl of from one to six carbon atoms;

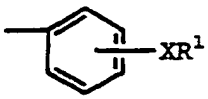




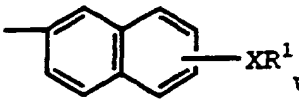
wherein $R^6$, $R^7$, $R^8$, or $R^9$ are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, halogen, or trifluoromethyl,



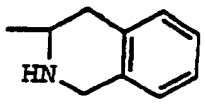
,



wherein $R^1$ and X are as defined above,



wherein $R^1$ and X are as defined above,



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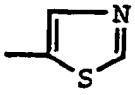

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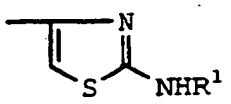
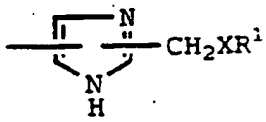
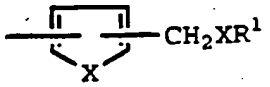
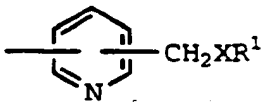
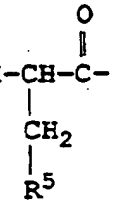
 wherein $R^1$ is as defined above,

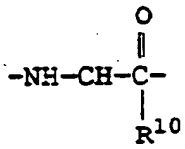
 wherein X and $R^1$ are as defined above,

 wherein $R^1$ and X are as defined above, or

 wherein $R^1$ and X are as defined above;

G is  wherein $R^5$ is as defined above,

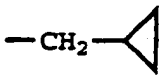
or

 wherein $R^{10}$ is

hydrogen,

alkyl of from one to six carbon atoms,

$-CO_2CH_3$,

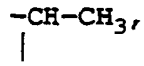
 ,

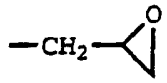
$-CH_2-CH=CH_2$,

$-CH_2-C\equiv CH$,

$-CH_2-CN$,

$-CH_2-OH$,





$-CH_2-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

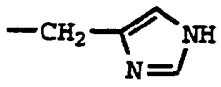
$-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

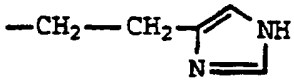
defined above,

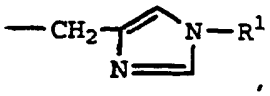
$-CH_2-CH_2CH_2CH_2-NH_2$,

$-CH_2-CH_2-S(O)_n-R^1$ wherein n and $R^1$ are as defined above,

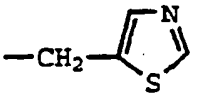
$-(CH_2)_n-CONH_2$ wherein n is as defined above,



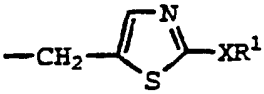




wherein $R^1$ is as defined above,

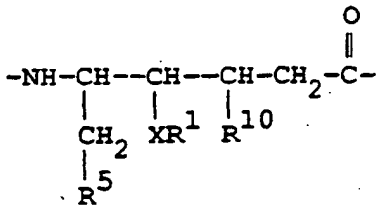


,or

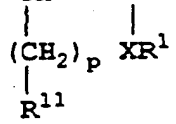


wherein X and $R^1$ are as defined above;

alternatively, E-G is

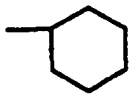


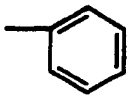
wherein $R^1$, X, $R^5$, and $R^{10}$ are as defined above;

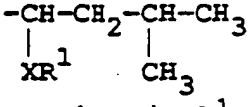
J is  wherein $R^{11}$ is

hydrogen,

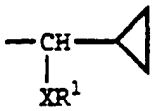
alkyl,

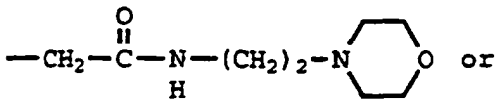
 , or

 ,

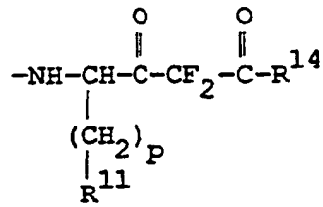
$R^{12}$ is 

wherein $R^1$ and X are as defined above,

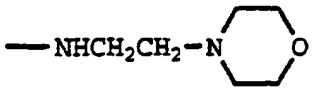
 wherein $R^1$ and X are as defined above,

 or

$-CH_2-OC_2H_5$ and $R^1$ and X are as defined above and p is zero or an integer of one, or



wherein $R^{14}$ is

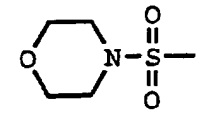


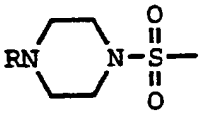
or

$-OC_2H_5$

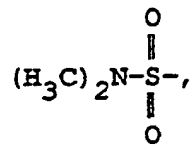
and $R^{11}$ and p are as defined above;
provided $R^1$ with the exclusion of $R^1$ being hydrogen is encompassed within the definition of at least one of A, E, G, or J; or a pharmaceutically acceptable salt thereof.

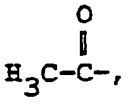
2. A compound according to Claim 1, in which A is

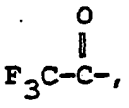


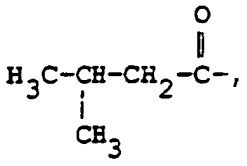


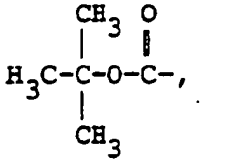
wherein R is hydrogen or alkyl of from one to six carbon atoms,

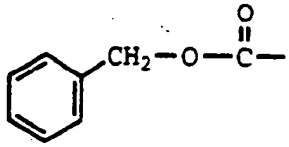


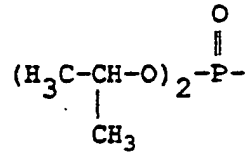


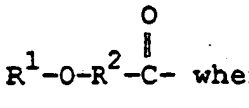




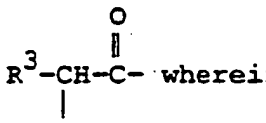






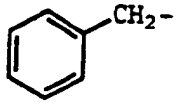


wherein $R^1$ is



wherein $R^3$ is

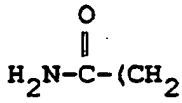
hydrogen,



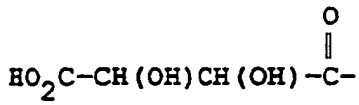
$CH_3$-,

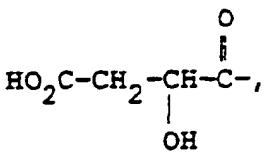
$H_2N-(CH_2)_4$-,

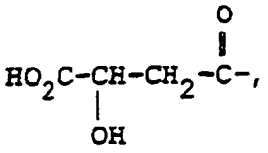
$HO_2C-(CH_2)_m$- wherein m is an integer of 1 of 2, or

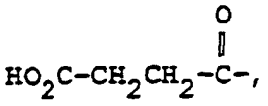


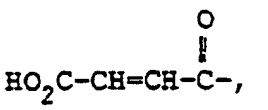
wherein m is as defined above,

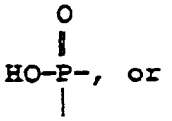


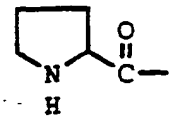






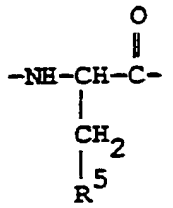


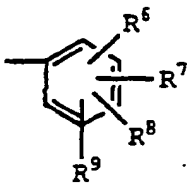




and

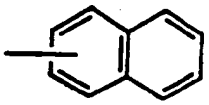
$R^2$ is alkyl of from one to six carbon atoms;

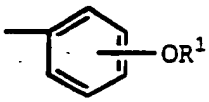
E is  wherein $R^5$ is



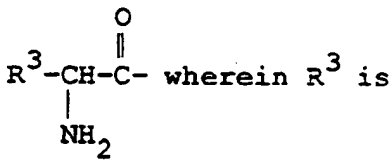
wherein $R^6$, $R^7$, $R^8$, or $R^9$ are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxyl of from one to six carbon

atoms, halogen or trifluoromethyl,

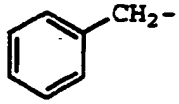
 or



wherein $R^1$ is hydrogen,

 wherein $R^3$ is

hydrogen,

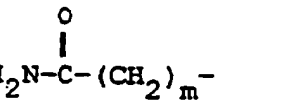


$CH_3$-,

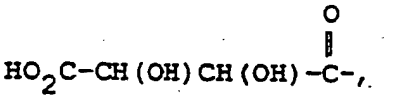
$H_2N-(CH_2)_4$-,

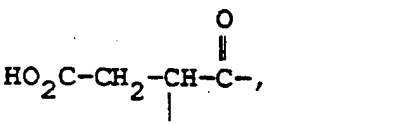
$HO_2C-(CH_2)_m$-

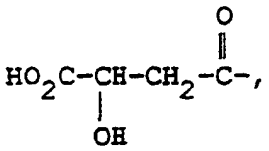
wherein m is an integer of 1 or 2, or

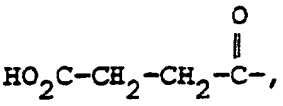


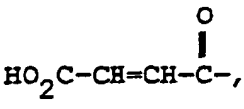
wherein m is as defined above,

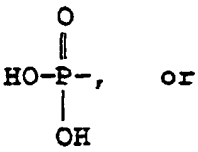


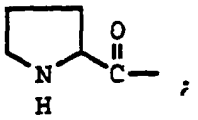


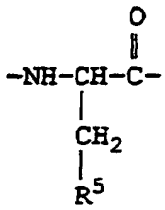


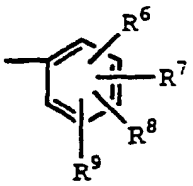




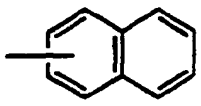


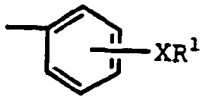


G is  wherein $R^5$ is

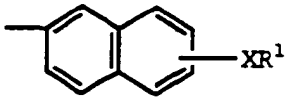


wherein $R^6$, $R^7$, $R^8$, or $R^9$ are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, halogen, or trifluoromethyl,

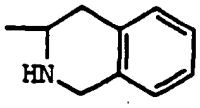


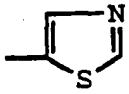


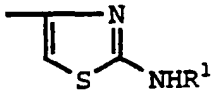
wherein X is O, S, or NH and $R^1$ is as defined above



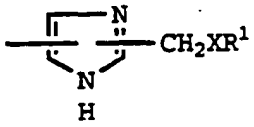
wherein $R^1$ and X are as defined above,



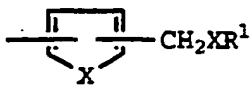




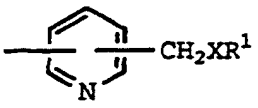
wherein $R^1$ is as defined above,



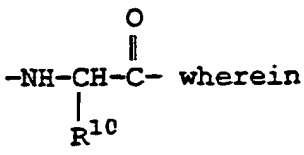
wherein X and $R^1$ are as defined above,



wherein $R^1$ and X are as defined above,



wherein $R^1$ and X are as defined above, or

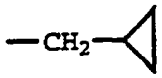


wherein $R^{10}$ is

hydrogen,

alkyl of from one to six carbon atoms,

$-CO_2CH_3$,

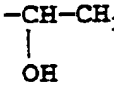


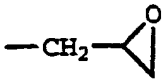
$-CH_2-CH=CH_2$,

$-CH_2-C\equiv CH$,

$-CH_2-CN$,

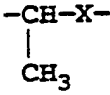
$-CH_2-OH$,





$-CH_2-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

$-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

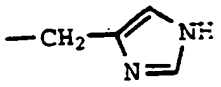


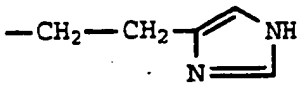
wherein X and $R^1$ are as defined above,

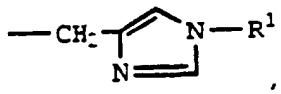
$-CH_2-CH_2CH_2CH_2-NH_2$,

$-CH_2-CH_2-S(O)_n-R^1$ wherein n is zero or an integer of 1 or 2 and $R^1$ is as defined above,

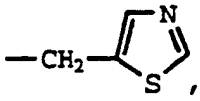
$-(CH_2)_n-CONH_2$ wherein n is as defined above,

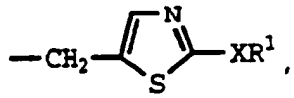






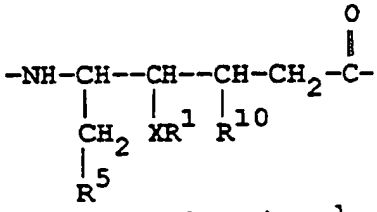
wherein $R^1$ is as defined above,



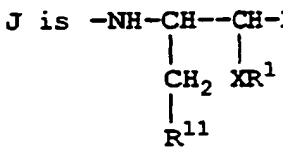


wherein X and $R^1$ are as defined above;

alternatively, E-G is

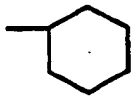


wherein $R^1$, X, $R^5$, and $R^{10}$ are as defined above;

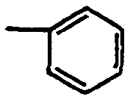
J is  wherein $R^{11}$ is

hydrogen,

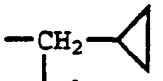
alkyl,



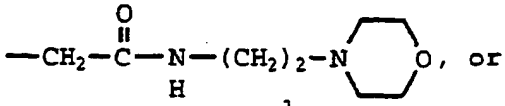
, or



$R^{12}$ is $-CH(OR^1)-CH_2-CH(CH_3)-CH_3$ wherein $R^1$ is as defined above,

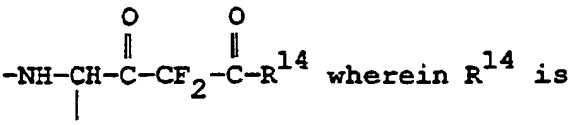


wherein $R^1$ is as defined above,

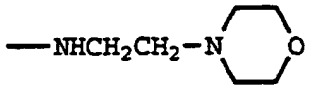


$-CH_2-OC_2H_5$ and $R^1$ and X are as defined above

or



wherein $R^{14}$ is

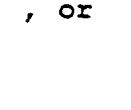


or

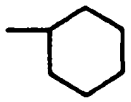
$-OC_2H_5$ and $R^{11}$ is as defined above; provided $R^1$ with the exclusion of $R^1$ being hydrogen is encompassed within the definition of at least one of A, E, G, or J.

3. A compound according to Claim 2, in which J is $-NH-CH(CH_2R^{11})-CH(XR^1)-R^{12}$ wherein $R^{11}$ is

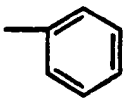
alkyl,



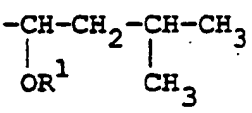
, or

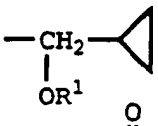


, or

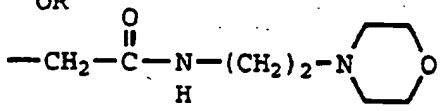


,

$R^{12}$ is 

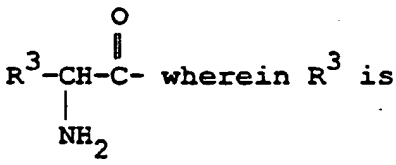


or

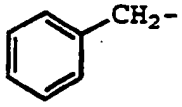


and

$R_1$ is hydrogen,



wherein $R^3$ is hydrogen,

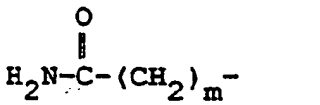


$CH_3$-,

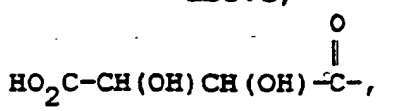
$H_2N-(CH_2)_4$-,

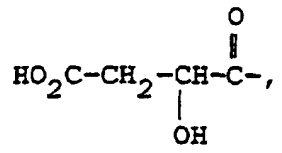
$HO_2C-(CH_2)_m$-

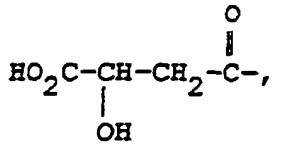
wherein m is an integer of 1 or 2, or

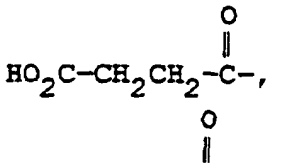


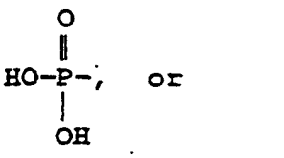
wherein m is as defined above,

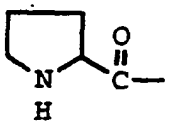


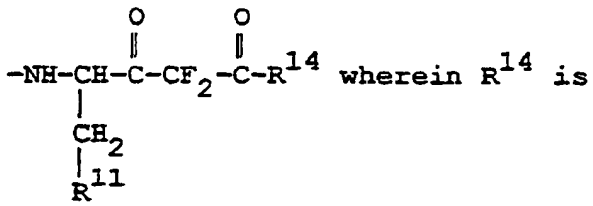


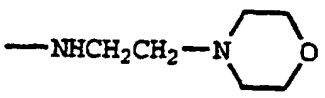






 and X is O, S, or NH, or

 wherein $R^{14}$ is

 , or

$-OC_2H_5$ and

$R^{11}$ is as defined above.

4. A compound according to Claim 3 selected from the group consisting of:

SMO-Phe-Ser(Phe)-CAD;

SMO-Phe-Ser(Gln)-CAD;

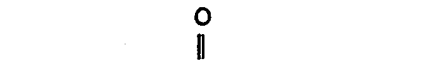
SMO-Phe-Ser(Pro)-CAD;
SMO-Phe-Ser(Glu)-CAD;
SMO-Phe-Ser(Lys)-CAD;
SMO-Phe-Ser(Asp)-CAD;
SMO-Phe-Ser(Gly)-CAD;
SMO-Phe-Ser(Ala)-CAD;
SMO-Phe-Ser($COCH_2CH_2CO_2H$)-CAD;
SMO-Phe-Ser(P(O)$(OH)_2$)-CAD;
SMO-Phe-Ser(COCH(OH)CH(OH)$CO_2H$)-CAD;
SMO-Phe-Thr(Phe)-CAD;
SMO-Phe-Thr(Gln)-CAD;
SMO-Phe-Thr(Pro)-CAD;
SMO-Phe-Thr(Glu)-CAD;
SMO-Phe-Thr(Lys)-CAD;
SMO-Phe-Thr(Asp)-CAD;
SMO-Phe-Thr(Gly)-CAD;
SMO-Phe-Thr(Ala)-CAD;
SMO-Phe-Thr($COCH_2CH_2CO_2H$)-CAD;
SMO-Phe-Thr(P(O)$(OH)_2$)-CAD;
SMO-Phe-Thr(COCH(OH)CH(OH)$CO_2H$)-CAD;
Boc-Tyr(Phe)-Pgy-CAD;
Boc-Tyr(Gln)-Pgy-CAD;
Boc-Tyr(Pro)-Pgy-CAD;
Boc-Tyr(Glu)-Pgy-CAD;
Boc-Tyr(Lys)-Pgy-CAD;
Boc-Tyr(Asp)-Pgy-CAD;
Boc-Tyr(Gly)-Pgy-CAD;
Boc-Tyr(Ala)-Pgy-CAD;
Boc-Tyr($COCH_2CH_2CO_2H$)-Pgy-CAD;
Boc-Tyr(P(O)(OH)CH(OH)$CO_2H$)-Pgy-CAD;
Boc-Tyr(COCH(OH)CH(OH)$CO_2H$)-Pgy-CAD;
SMO-Phe-Hse(Phe)-CAD;
SMO-Phe-Hse(Gln)-CAD;
SMO-Phe-Hse(Pro)-CAD;
SMO-Phe-Hse(Glu)-CAD;
SMO-Phe-Hse(Lys)-CAD;

SMO-Phe-Hse(Asp)-CAD;
SMO-Phe-Hse(Gly)-CAD;
SMO-Phe-Hse(Ala)-CAD;
SMO-Phe-Hse($COCH_2CH_2CO_2H$)-CAD;
SMO-Phe-Hse(P(O)$(OH)_2$)-CAD;
SMO-Phe-Hse(COCH(OH)CH(OH)$CO_2H$)-CAD;
SMO-Phe-Mal-CAD(2·Phe);
SMO-Phe-Mal-CAD(2·Gln);
SMO-Phe-Mal-CAD(2·Pro);
SMO-Phe-Mal-CAD(2·Glu);
SMO-Phe-Mal-CAD(2·Lys);
SMO-Phe-Mal-CAD(2·Asp);
SMO-Phe-Mal-CAD(2·Gly);
SMO-Phe-Mal-CAD(2·Ala);
SMO-Phe-Mal-CAD(2·$COCH_2CH_2CO_2H$);
SMO-Phe-Mal-CAD(2·P(O)$(OH)_2$);
SMO-Phe-Mal-CAD(2·COCH(OH)CH(OH)$CO_2H$);
SMO-Phe-Atm-CAD(2·Phe);
SMO-Phe-Atm-CAD(2·Gln);
SMO-Phe-Atm-CAD(2·Pro);
SMO-Phe-Atm-CAD(2·Glu);
SMO-Phe-Atm-CAD(2·Lys);
SMO-Phe-Atm-CAD(2·Asp);
SMO-Phe-Atm-CAD(2·Gly);
SMO-Phe-Atm-CAD(2·Ala);
SMO-Phe-Atm-CAD(2·$COCH_2CH_2CO_2H$);
SMO-Phe-Atm-CAD(2·P(O)$(OH)_2$);
SMO-Phe-Atm-CAD(2·COCH(OH)CH(OH)$CO_2H$);
SMO-Phe-Atm(Phe)-CAD;
SMO-Phe-Atm(Gln)-CAD;
SMO-Phe-Atm(Pro)-CAD;
SMO-Phe-Atm(Glu)-CAD;
SMO-Phe-Atm(Lys)-CAD;
SMO-Phe-Atm(Asp)-CAD;
SMO-Phe-Atm(Gly)-CAD;
SMO-Phe-Atm(Ala)-CAD;

SMO-Phe-Atm($COCH_2CH_2CO_2H$)-CAD;

SMO-Phe-Atm($P(O)(OH)_2$)-CAD;

SMO-Phe-Atm($COCH(OH)CH(OH)CO_2H$)-CAD;

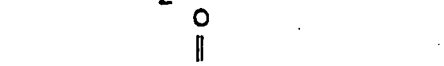


(Phe)O-$CH_2$-C-Phe-Alg-CAD;

(Gln)O-$CH_2$-C-Phe-Alg-CAD;

(Pro)O-$CH_2$-C-Phe-Alg-CAD;

(Glu)O-$CH_2$-C-Phe-Alg-CAD;



(Lys)O-$CH_2$-C-Phe-Alg-CAD;

(Asp)O-$CH_2$-C-Phe-Alg-CAD;

(Gly)O-$CH_2$-C-Phe-Alg-CAD;

(Ala)O-$CH_2$-C-Phe-Alg-CAD;

($HO_2CCH_2CH_2CO$)O-$CH_2$-C-Phe-Alg-CAD;

($(HO)_2P(O)$)O$CH_2$-C-Phe-Alg-CAD;

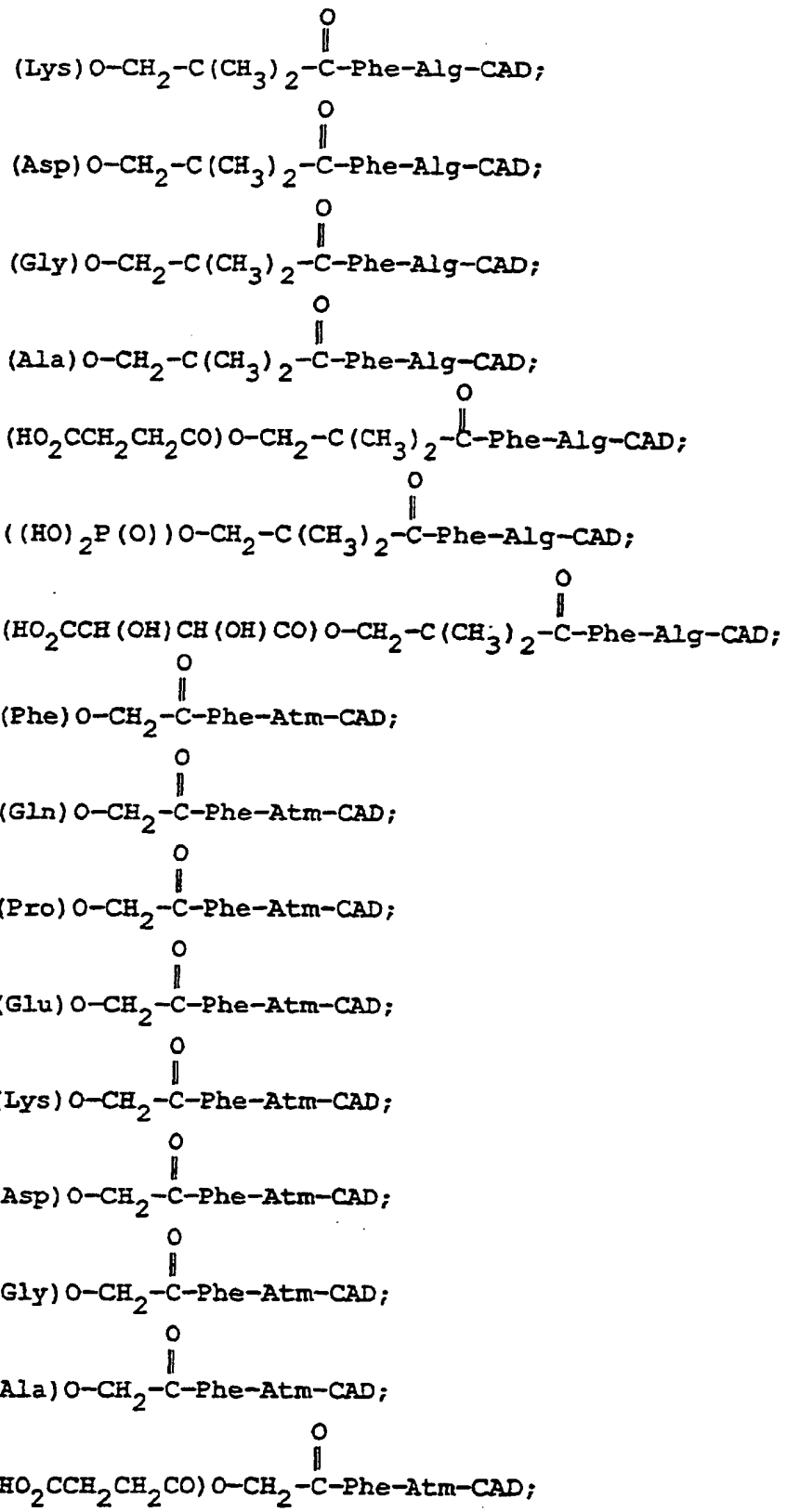
($HO_2CCH(OH)CH(OH)CO$)O$CH_2$-C-Phe-Alg-CAD;

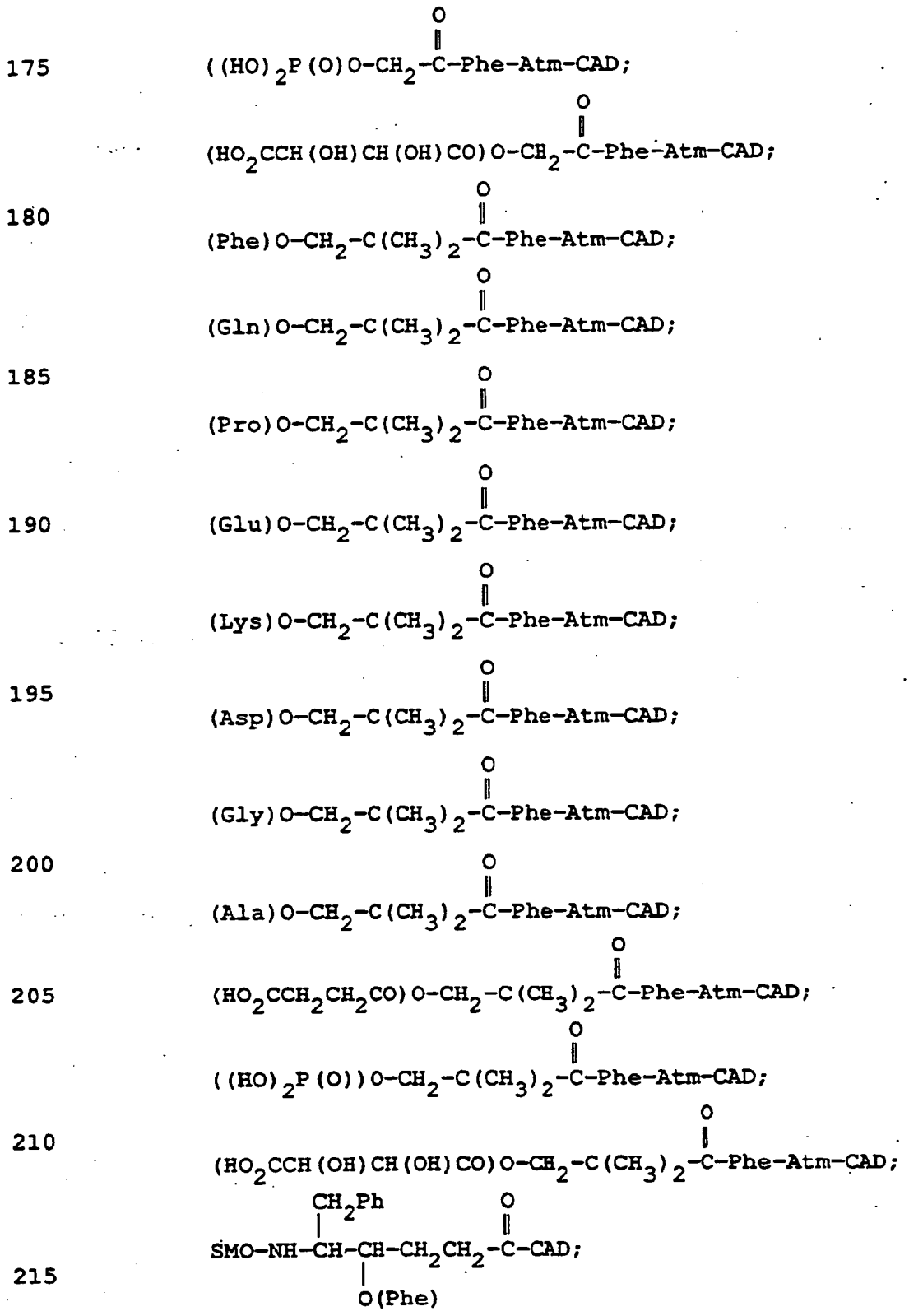
(Phe)O-$CH_2$-$C(CH_3)_2$-C-Phe-Alg-CAD;

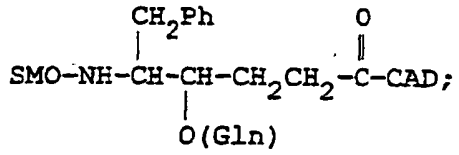
(Gln)O-$CH_2$-$C(CH_3)_2$-C-Phe-Alg-CAD;

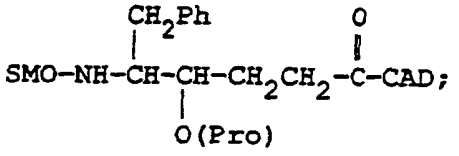
(Pro)O-$CH_2$-$C(CH_3)_2$-C-Phe-Alg-CAD;

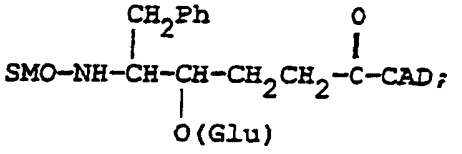
(Glu)O-$CH_2$-$C(CH_3)_2$-C-Phe-Alg-CAD;

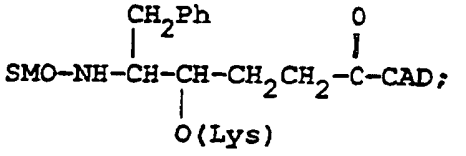

(Lys)O-CH2-C(CH3)2-C-Phe-Alg-CAD;
(Asp)O-CH2-C(CH3)2-C-Phe-Alg-CAD;
(Gly)O-CH2-C(CH3)2-C-Phe-Alg-CAD;
(Ala)O-CH2-C(CH3)2-C-Phe-Alg-CAD;
(HO2CCH2CH2CO)O-CH2-C(CH3)2-C-Phe-Alg-CAD;
((HO)2P(O))O-CH2-C(CH3)2-C-Phe-Alg-CAD;
(HO2CCH(OH)CH(OH)CO)O-CH2-C(CH3)2-C-Phe-Alg-CAD;
(Phe)O-CH2-C-Phe-Atm-CAD;
(Gln)O-CH2-C-Phe-Atm-CAD;
(Pro)O-CH2-C-Phe-Atm-CAD;
(Glu)O-CH2-C-Phe-Atm-CAD;
(Lys)O-CH2-C-Phe-Atm-CAD;
(Asp)O-CH2-C-Phe-Atm-CAD;
(Gly)O-CH2-C-Phe-Atm-CAD;
(Ala)O-CH2-C-Phe-Atm-CAD;
(HO2CCH2CH2CO)O-CH2-C-Phe-Atm-CAD;

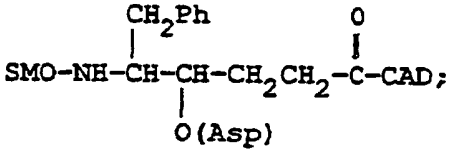


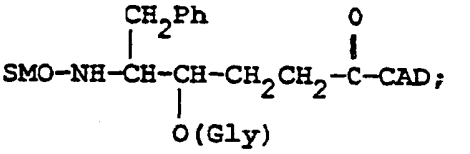


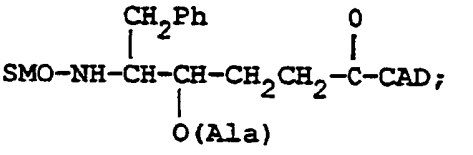


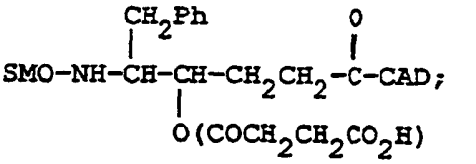


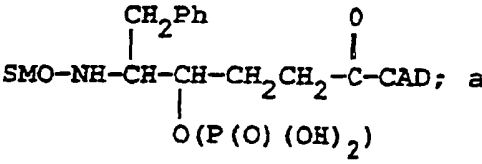


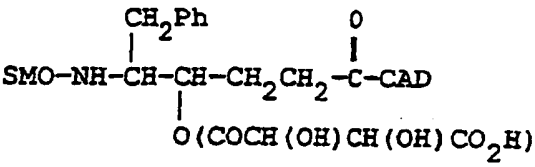




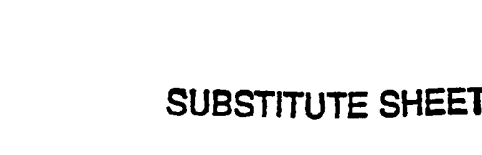








and



.

5. A method of treating renin-associated hypertension comprising administering to a host suffering therefrom a therapeutically effect amount of a compound according to Claim 1 in unit dosage form.

6. A pharmaceutical composition adapted for administration as an antihypertensive agent comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

7. A method of treating hyperaldosteronism comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

8. A pharmaceutical composition adapted for administration as an agent for treating hyperaldosteronism comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

9. A method of treating congestive heart failure comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

10. A pharmaceutical composition adapted for administration as an agent for treating congestive heart failure comprising a therapeutically effective amount of a compound

according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

11. A method of treating glaucoma comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

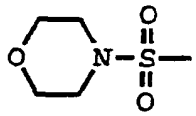
12. A pharmaceutical composition adapted for administration as an agent for treating glaucoma comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

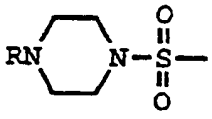
13. A method of preparing a compound having the Formula I

A-E-G-J

I

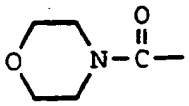
wherein A is

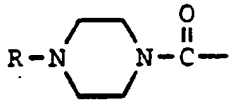




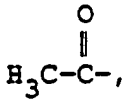
wherein R is hydrogen or alkyl of from one to six carbon atoms,

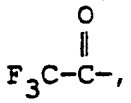
wherein R is as defined above,

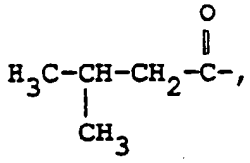


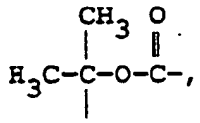


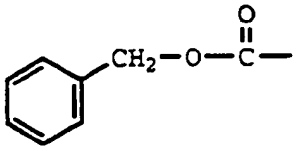
wherein R is as defined above,

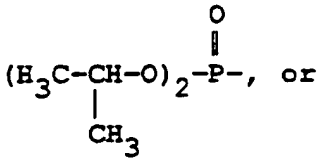


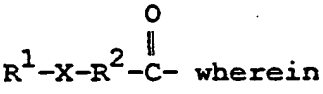




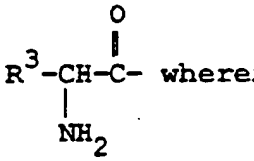




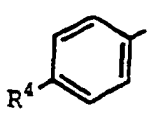




wherein $R^1$ is hydrogen,



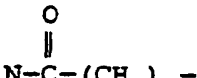
wherein $R^3$ is hydrogen,

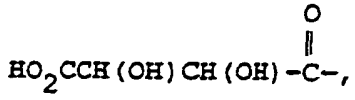
 wherein n is zero or an integer of 1 or 2 and $R^4$ is hydrogen or hydroxyl,

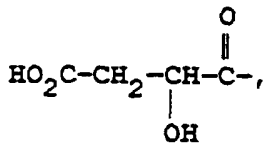
$CH_3-$,

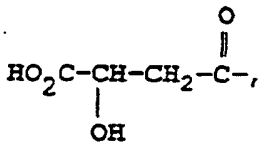
$H_2N-(CH_2)_4-$,

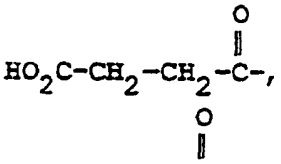
$HO_2C-(CH_2)_m-$ wherein m is an integer of 1 or 2, or

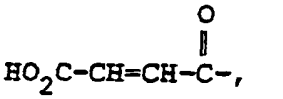
 wherein m is as defined above,

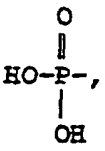


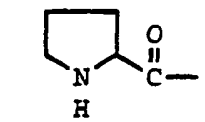


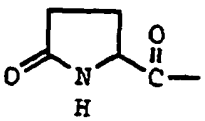




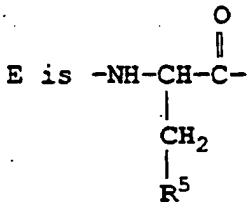


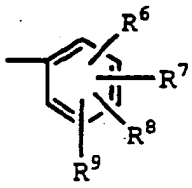


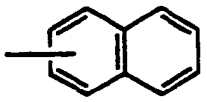
 , or

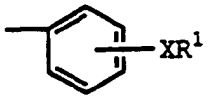


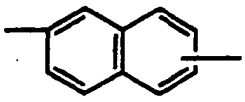
X is O, S, or NH, and
$R^2$ is alkyl of from one to six carbon atoms;

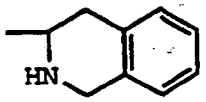
E is  wherein $R^5$ is

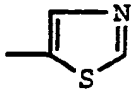
 wherein $R^6$, $R^7$, $R^8$, or $R^9$ are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, halogen, or trifluoromethyl,

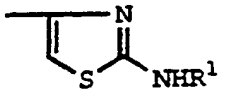
 ,

 wherein $R^1$ and X are as defined above,

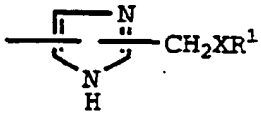
 wherein $R^1$ and X are as defined above,

 ,

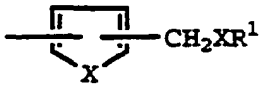




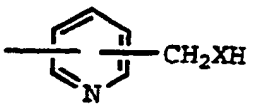
wherein $R^1$ is as defined above,



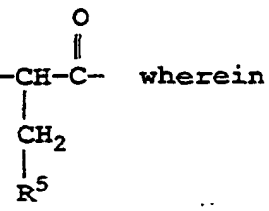
wherein X and $R^1$ are as defined above,



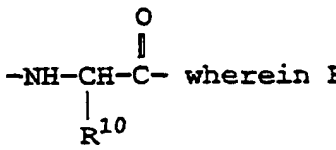
wherein $R^1$ and X are as defined above, or



wherein $R^1$ and X are as defined above;

G is  wherein $R^5$ is as defined above,

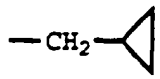
or

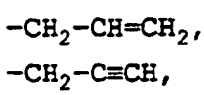
 wherein $R^{10}$ is

hydrogen,

alkyl of from one to six carbon atoms,

$-CO_2CH_3$,





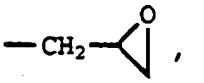
$-CH_2-CH=CH_2$,

$-CH_2-C\equiv CH$,

$-CH_2-CN$,

$-CH_2-OH$,

$-CH(OH)-CH_3$,



$-CH_2-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

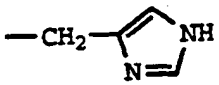
$-CH_2X-R^1$ wherein X and $R^1$ are as defined above,

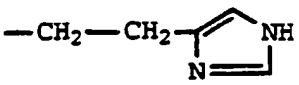
$-CH(CH_3)X-R^1$ wherein X and $R^1$ are as defined above,

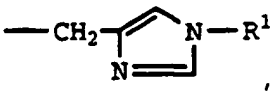
$-CH_2-CH_2CH_2CH_2-NH_2$,

$-CH_2-CH_2-S(O)_n-R^1$ wherein n and $R^1$ are as defined above,

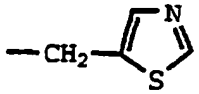
$-(CH_2)_n-CONH_2$ wherein n is as defined above,



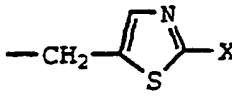




wherein $R^1$ is as defined above,

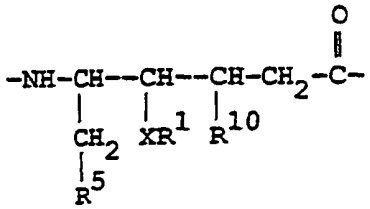


, or

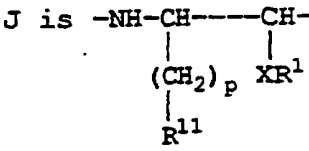


wherein X and $R^1$ are as defined above;

alternatively, E-G is

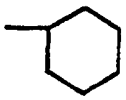


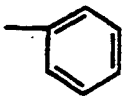
wherein $R^1$, X, $R^5$, and $R^{10}$ are as defined above;

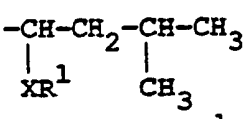
J is  wherein $R^{11}$ is

hydrogen,

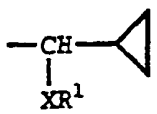
alkyl,

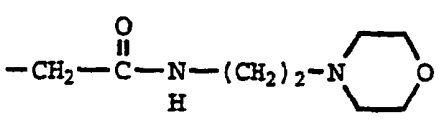
 , or

 ,

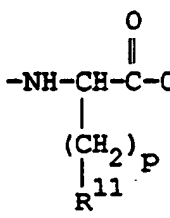
$R^{12}$ is 

wherein $R^1$ and X are as defined above,

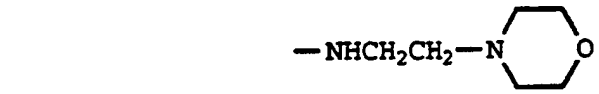
 wherein $R^1$ and X are as defined above,

 or

$-CH_2-OC_2H_5$ and $R^1$ and X are as defined above and p is zero or an integer of one, or



wherein $R^{14}$ is



or

$-OC_2H_5$

and $R^{11}$ and p are as defined above;

provided $R^1$ with the exclusion of $R^1$ being hydrogen is encompassed within the definition of at least one of A, E, G, or J; or a pharmaceutically acceptable salt thereof comprises:

a) coupling a compound of Formula II

$$A'-E'-G'-J'$$

II

wherein A', E', G', and J' are as defined above for A, E, G, and J provided $R^1$ is hydrogen and is encompassed within the definition of at least one of A', E', G', or J' with a compound of Formula III

$$R^{1a}-XH$$

III

wherein $R^{1a}$ is as defined above for $R^1$ but excluding $R^1$ is hydrogen and providing any basic

or acidic groups contain conventional protecting groups and X is as defined above to afford a compound of Formula IV

215 A''-E''-G''-J''

IV

wherein A'', E'', G'', and J'' are as defined above for A, E, G, and J provided $R^{1a}$ is as defined above and is encompassed within the 220 definition of at least one of A'', E'', G'' or J'';

b) a compound of Formula IV is deprotected in a conventional manner to afford a compound of Formula I; and if desired, 225 converting a compound of Formula I to a corresponding pharmaceutically acceptable salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable salt to a compound of Formula I by 230 conventional means.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/07463

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 K 5/06, 11/00, C 07 C 295/26, A 61 K 37/64, 31/535, C 07 K 5/02

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| IPC5 | A 61 K; C 07 K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category * | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | WO, A2, 9012804 (THE UPJOHN COMPANY)<br>1 November 1990,<br>see the claims | 1-4,6,8,<br>10,12,<br>13 |
| A | EP, A1, 0315815 (WARNER-LAMBERT COMPANY)<br>17 May 1989,<br>see the whole document | 1-4,6,8,<br>10,12,<br>13 |
| A | US, A, 5036053 (HIMMELSBACH ET AL)<br>30 July 1991,<br>see the whole document | 1-4,6,8,<br>10,12,<br>13 |

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 17th December 1992 | 05. 01. 93 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | Elisabeth Carlborg |



See notes on accompanying sheet

| III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) | | |
|---|---|---|
| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No |
| A | EP, A1, 0399556 (WARNER-LAMBERT COMPANY)<br>28 November 1990,<br>see the whole document | 1-4,6,8,<br>10,12,<br>13 |

INTERNATION[redacted] SEARCH REPORT

International application No.
PCT/US[redacted]07463

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5,7,9,11
because they relate to subject matter not required to be searched by this Authority, namely:
see PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 92/07463

SA 64415

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/12/92
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| WO-A2- 9012804 | 01/11/90 | AU-D- | 5407190 | 16/11/90 |
| | | EP-A- | 0468998 | 05/02/92 |
| | | JP-T- | 4504716 | 20/08/92 |
| EP-A1- 0315815 | 17/05/89 | AU-D- | 2728188 | 23/05/89 |
| | | US-A- | 5034512 | 23/07/91 |
| | | WO-A- | 89/03820 | 05/05/89 |
| US-A- 5036053 | 30/07/91 | AU-B- | 625456 | 09/07/92 |
| | | AU-D- | 3463389 | 30/11/89 |
| | | EP-A- | 0343654 | 29/11/89 |
| | | JP-A- | 2067297 | 07/03/90 |
| EP-A1- 0399556 | 28/11/90 | AU-B- | 625354 | 09/07/92 |
| | | AU-D- | 5590890 | 29/11/90 |
| | | CA-A- | 2017552 | 26/11/90 |
| | | JP-A- | 3086870 | 11/04/91 |

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

EPO FORM P0479